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Design, synthesis, and biological evaluation of Mannich bases of heterocyclic chalcone analogs as cytotoxic agents

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ABSTRACT

The chalcone skeleton (1,3-diphenyl-2-propen-1-one) is a unique template that is associated with various biological activities. We synthesized Mannich bases of heterocyclic chalcones (**9**–**47**) using a one-step Claisen–Schmidt condensation of heterocyclic aldehydes with Mannich bases of acetophenones, and tested the target compounds for cytotoxicity against three human cancer cell lines (prostate, PC-3; breast, MCF-7; nasopharynx, KB) and a multi-drug resistant subline (KB-VIN). Out of the 39 chalcones synthesized, 31 compounds showed potent activity against at least one cell line with IC_{50} values ranging from 0.03 to 3.80 μg/mL. Structure–activity relationships (SAR) are also discussed.

1. Introduction

Chalcones, which are considered to be precursors of flavonoids and isoflavonoids, are abundant in edible plants. Chemically they are open-chain flavonoids in which the two aromatic rings are joined by a three-carbon α,β-unsaturated carbonyl system (1,3-diphenyl-2-propen-1-one). Chalcones exhibit many pharmacological activities, including anti-leishmanial,[1] anti-inflammatory,[2–4] anti-mitotic,[5] anti-invasive,[6,7] anti-tuberculosis,[8] anti-fungal,[9] $CyLT_1$ (LTD_4) receptor antagonist,[10] anti-malarial,[11,12] anti-plasmodial, immunosupressive, cytotoxic, anti-tumor, and anti-oxidant properties,[13] and modulation of P-glycoprotein-mediated multi-drug resistance.[14] Recent studies have shown that chalcones inhibit cancer cell proliferation, are effective agents in vivo against skin carcinogenesis[15,16] and induce apoptosis in various cell types, including breast cancers.[17,18] Several oxygenated chalcones, bischalcones, and some quinolinyl chalcone analogs reportedly show anti-malarial activity.[19,20]

Amodiaquine, amopyroquine, tebuquine, and *tert*-butylamodiaquine, which are semi-synthetic Mannich base derivatives of chloroquine,[21] and artemisin derivatives bearing Mannich bases showed potent in vitro and in vivo anti-malarial activity.[22] Mannich bases of phenolic azobenzenes demonstrated cytotoxic activity,[23] and various Mannich base analogs of chalcones exhibited potent cytotoxicity against murine P338 and L1210 leukemia cells as well as several human tumor cell lines.[24] Mannich bases have been associated with increased bioactivity.[25] The presence of a Mannich base group in chalcones and other compound types may increase biological potency due to the greater number of molecular sites for electrophilic attack by cellular constituents, as well as due to the cascade effect of preferential chemosensitization.

Heterocyclic chalcones play important roles as anti-ulcer, herbicidal, anti-bacterial, analgesic, sedative, anti-phlogistic and virucidal agents.[26] However, to the best of our knowledge, no literature exists on the synthesis and biological evaluation of Mannich bases of heterocyclic chalcones. Aminoalkylation of aromatic substrates by the Mannich reaction has considerable importance for the synthesis and modification of biologically active compounds. This technique provides convenient access to many useful synthetic building blocks, because the resulting amino group can be easily converted to various functionalities, particularly, to quaternary ammonium salts to increase water solubility. Accordingly, we synthesized 39 Mannich base derivatives of heterocyclic chalcones, based on the above pharmacological importance of the chalcone moiety.

Herein, we describe the synthesis and in vitro biological evaluation of Mannich bases of heterocyclic chalcones with different substitution patterns in the B-ring, together with a discussion of structure–activity relationships. All new analogs were tested for cytotoxic activity against PC-3 (prostate cancer), MCF-7 (human breast cancer), KB (nasopharyngeal carcinoma), and KB-VIN (vincristine-resistant KB subline) to obtain preliminary biological

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profiles of this compound series that will be useful in the further design and development of Mannich bases of heterocyclic chalcones.

2. Chemistry

As shown in Scheme 1, compound **1** underwent regioselective reaction with an alkyl halide (ethyl iodide, methyl iodide, isopropyl bromide, or prenyl bromide) at the non hydrogen-bonded phenol in the presence of K_2CO_3 in dry acetone at 80 °C to yield 4-alkoxy-substituted acetophenones **2a**, **3a**, **4a**, and **5a**, respectively. These four acetophenones and **1** were reacted with morpholine and 37% formaldehyde in EtOH at 120 °C for 18–22 h to provide C-3 or C-5 substituted Mannich base derivatives (**1a**, **2b/c**, **3b/c**, **4b/c**, and **5b**) (Scheme 1). Similar reactions of 4-hydroxyacetophenone **6** and 3-hydroxyacetophenone **7** gave mono- (**6a**, **7a**, and **7b**) and di-substituted (**6b** and **7c**) Mannich base derivatives. 3-Hydroxy-4-methoxybenzaldehyde **8** was reacted separately with piperidine and morpholine to obtain C-2 Mannich base derivatives **8a** and **8b**, respectively.

The designed target compounds (**9**–**42**) depicted in Scheme 2 were obtained by reacting **2b**, **2c**, **3b**, **3c**, **4b**, **4c**, **5b**, **6a**, **6b**, **7a**, **7b**, and **7c** (Mannich bases of acetophenones **2a**–**7**) with various heterocyclic aldehydes under Claisen–Schmidt conditions using 30% KOH in MeOH at room temperature. In addition, **8a** and **8b** (Mannich bases of benzaldehyde **8**) were condensed with 3′-methyl- and 4′-methylacetophenone, 2-acetylthiophene, 2-acetylfuran, and 3-acetylpyridine under similar conditions to yield **43**–**47**, respectively, in good yields.

3. Results and discussion

The 39 Mannich bases of heterocyclic chalcones were evaluated for cytotoxic activity against four human cancer cell lines (PC-3, MCF-7, KB, and KB-VIN). The results are shown in Table 1.

Among analogous compounds **9**–**12**, analog **9** showed significant cytotoxic activity against all four cell lines, with EC_{50} values of 0.95 (PC-3), 0.08 (MCF-7), 1.54 (KB), and 0.80 (KB-VIN) μg/mL. Compounds **10** and **11** showed significant activity against MCF-7 and KB-VIN cell lines (EC_{50} 0.25/0.66 and 1.13/1.45 μg/mL, respectively) and moderate cytotoxicity against PC-3 (only **11**) and KB (only **10**). Compound **12** showed moderate activity only against the MCF-7 cell line. Compound **9** was more active than **10**, although they have only one structural difference. Both compounds possess a 2-pyridyl B-ring but have a hydroxy and methoxy group, respectively, at the A-ring C-4′ position. Thus, from an SAR viewpoint, the hydroxy functionality is responsible for enhancing cytotoxic activity in **9**.

Analogs **13**–**18**, with a C-4′ ethyl group and various phenyl and heterocyclic B-rings, showed weak activity or no activity against the four cell lines with EC_{50} values ranging from 3.14 to 20.00 μg/mL. Interestingly, compounds **19** and **20** were much more potent [EC_{50} 0.84 and 0.78 (PC-3). 0.10 and 0.03 (MCF-7) μg/mL, respectively] than the corresponding **13** and **17**. The two pairs of compounds are structurally identical, except for a C-4′ methyl group in **19** and **20** rather than a C-4′ ethyl group in **13** and **17**. This difference clearly indicates that, among these compounds, the C-4′ methoxy group in ring A is of great importance to the activity. Analog **24**, which has a C-4′ isopropoxy group, showed significant potency only against MCF-7 cells (EC_{50} 0.24 μg/mL); however, it was more potent than **22** (EC_{50} 3.12 μg/mL), which has a C-4′-methoxy group, against this cell line. In addition, compounds **11** and **24** differ only in the position of the Mannich base group: C-3′ in the former and C-5′ in the latter. Compound **24** was somewhat more active than **11** against MCF-7 cells (EC_{50} 0.24 vs 0.66 μg/mL). Although there were no direct comparisons among analogs with C-4′ methoxy groups, compounds **19** and **20** (B-ring=3-pyridyl and phenyl, respectively; C-3′ Mannich base) were more active than **10** (B-ring=2-pyridyl; C-5′ Mannich base) against MCF-7 and PC-3 cells. These results indicate that a C-3′ Mannich base is preferable to a C-5′ Mannich base.

Compounds **25**–**32** have the same Mannich base at C-3′ and a hydroxy group at C-4′, but differ in the identity of the B-ring. Compounds **25**–**28**, which bear 2-, 3-, and 4-pyridyl and phenyl groups, respectively, were more potent against all cell lines (EC_{50} 0.10–2.11 μg/mL) than analogs with five-membered heterocycles (2-furan **29**, 2-thiophene **30**, 3-methyl-2-thiophene **31**, and 5-methyl-2-furan **32**). A similar comparison was found between **33** and **34**, which have two Mannich base groups in the A-ring. Compound **33**, with a six-membered 2-pyridyl B-ring, showed higher cytotoxicity against all four cell lines (EC_{50} 1.72, 1.34, 2.31, and 2.27 μg/mL, respectively) than **34**, which has a five-membered 3-methyl-2-thiophene group. These results indicate that a six-membered B-ring, particularly a pyridyl group, is important for enhanced cytotoxic activity.

Notably, compound **25**, with only one Mannich base group, was significantly more potent against all cell lines (EC_{50}0.31, 0.12, 0.73 and 0.30 μg/mL) than **33**, with two Mannich base groups (EC_{50} 1.72, 1.34, 2.31 and 2.27 μg/mL). Compound **25** was also generally more potent than **9**, which is structurally identical except for an added 2′-OH group.

The positions of the Mannich base and hydroxy group also had some effect on activity. Compounds **35**–**37** are positional isomers of **25**–**27**. In the former compounds, the Mannich base and hydroxyl are at C-3′ and C-4′, respectively, while in the latter compounds, these groups are at C-4′ and C-5′, respectively. Both sets of compounds were significantly active in all assays, but **25**–**27** were generally more potent than **35**–**37** (e.g., EC_{50} 0.12–0.73 μg/mL for **25**, EC_{50} 0.43–1.30 μg/mL for **35**). In addition, compound **33**, bearing two Mannich base groups at C-2′ and C-5′ and a hydroxy group at C-4′ was less potent than **42**, bearing two Mannich base groups at C-2′ and C-4′ and a hydroxyl at C-3′.

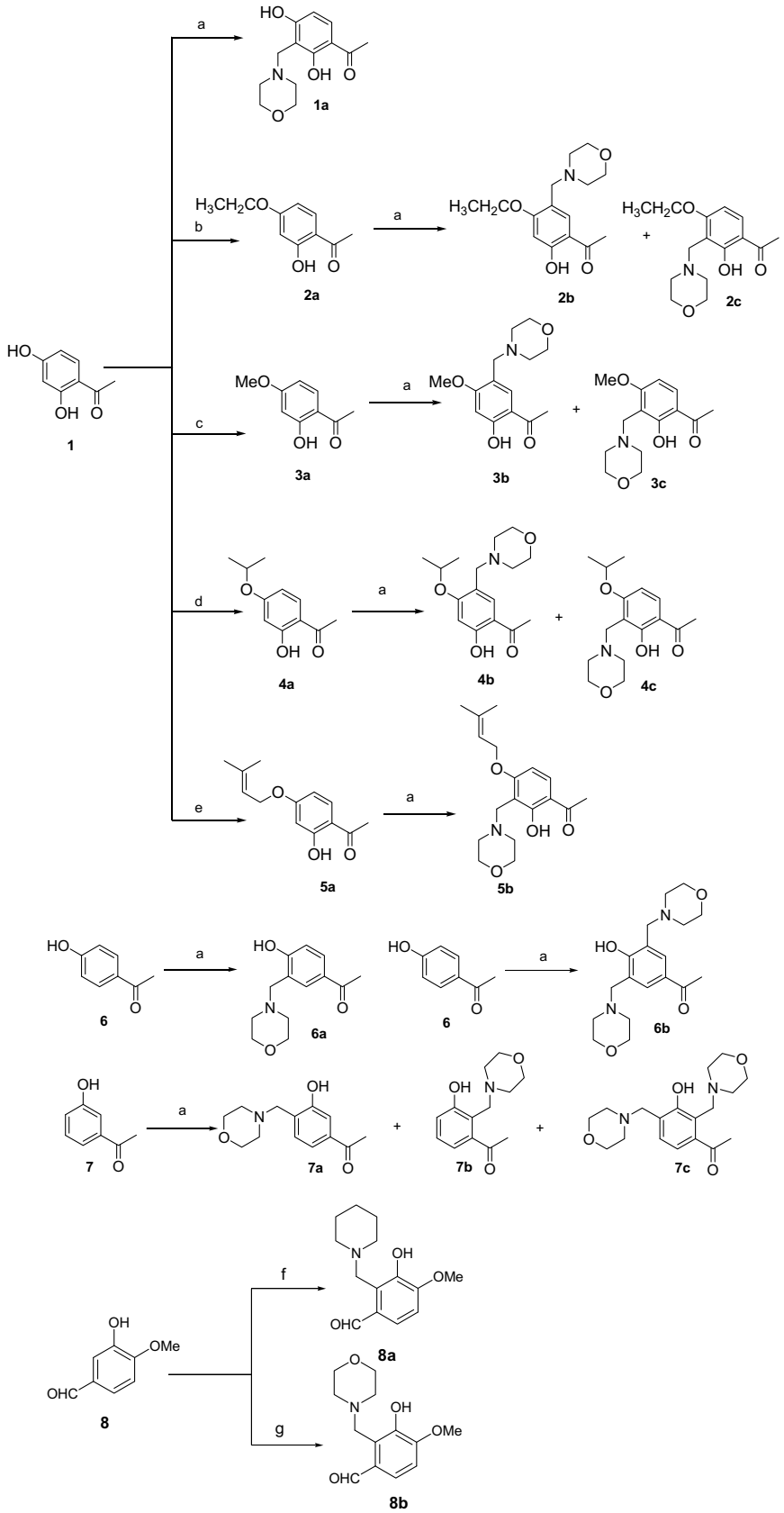
As previously found with analogs **29**–**31**, compounds **38**–**40**, which have five-membered B-rings (2-furan, 2-thiophene and 3-methyl-2-thiophene), showed little potency against the tested cell lines. However, compound **41**, which has a phenyl group as the B-ring, showed significant cytotoxic activity against all cell lines, with EC_{50} values of 0.33, 0.28, 0.83, and 0.36 μg/mL.

Compounds **43** and **45**–**47**, which have a Mannich base in the A-ring rather than B-ring, showed significant activity against MCF-7 cells with EC_{50}values of 0.42, 0.36, 0.11, 0.47, and 0.30 μg/mL, respectively, but showed varying potencies against the other three cell lines. Overall, compound **43** with a 3-methylphenyl A-ring showed greater cytotoxicity than **45**–**47** with 2-thiophenyl, 2-furanyl, and 3-pyridyl A-rings.

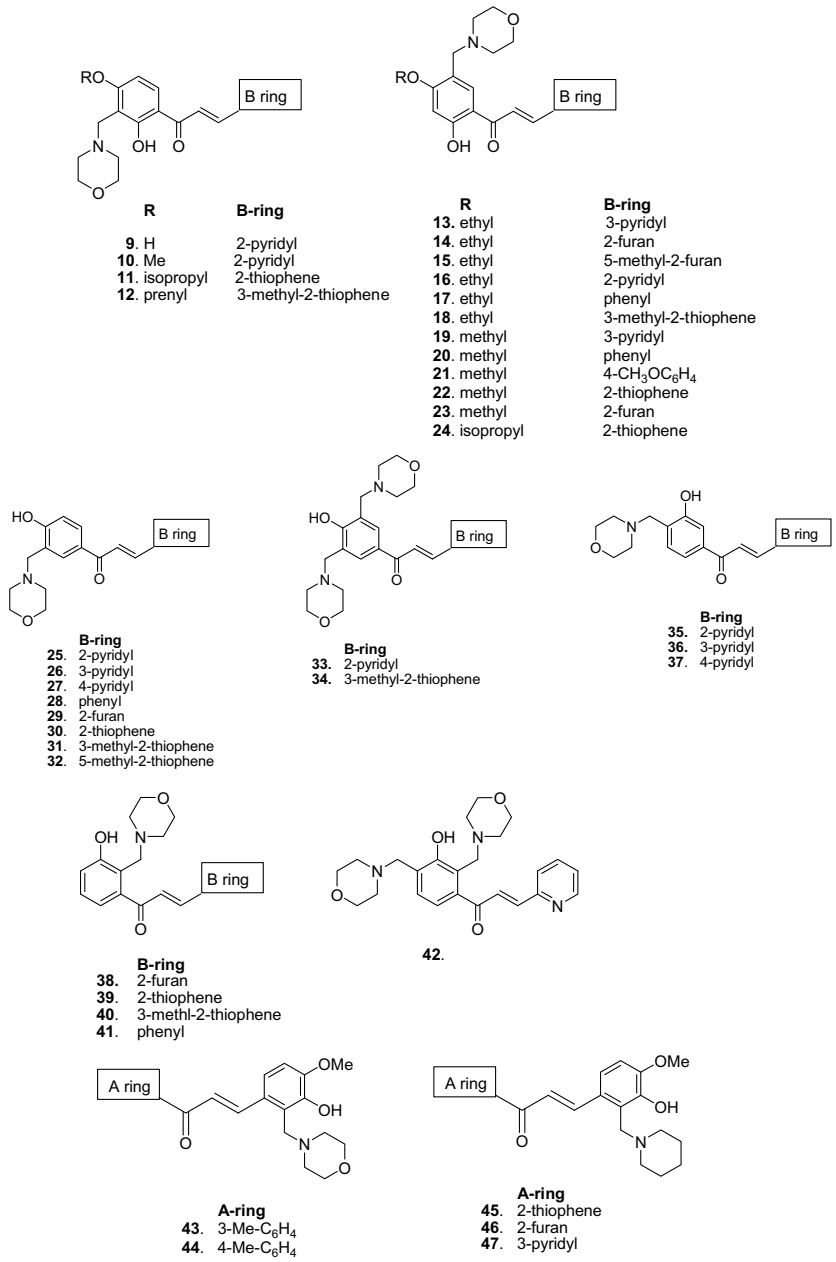
The following general observations were made from the study results. With the exception of **13**–**15**, **17**, **18**, **31**, and **34**, all synthesized heterocyclic chalcones showed cytotoxic activity (EC_{50} < 4 μg/mL) against at least one cell line. Compounds **25**, **27**, **41**, and **42** had EC_{50} values less than 1 μg/mL against all four cell lines, and **9**, **26**, **28**, **35**, and **43** against three cell lines. MCF-7 and PC-3 were generally more sensitive than KB and KB-VIN cell lines to these heterocyclic chalcones.

4. Conclusions

In summary, we designed and synthesized a series of Mannich bases of heterocyclic chalcones, which were structurally confirmed by IR, ^1H, ^{13}C NMR, EIMS, HREIMS and elemental analysis and evaluated their cytotoxicity against four human cancer cell lines (PC-3,



Scheme 1. Reagents and conditions: (a) HCHO, morpholine, reflux at 120 °C in 18–22 h; (b) MeI, Me_2CO, reflux at 80 °C in 6 h; (c) C_2H_5I, Me_2CO, reflux at 80 °C in 6 h; (d) isopropyl bromide, Me_2CO, reflux at 80 °C in 8 h; (e) prenyl bromide, Me_2CO, reflux at 80 °C in 6 h; (f) HCHO, piperidine, reflux at 120 °C in 18–22 h.



Scheme 2.

MCF-7, KB, and KB-VIN).The results showed that out of the 39 chalcones tested, 35 compounds showed potent activity against at least one cell line. The most active compounds are **9** and **20** with IC_{50} values of 0.08 and 0.03 μg/mL, respectively, against the MCF-7 cell line.

5. Experimental

5.1. Chemistry

Melting points were determined using a Buchi melting point apparatus B-540 and are uncorrected. IR spectra were determined on a Shimadzu FT-IR Prestige 21 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 spectrometer, using tetramethylsilane (TMS) as internal standard; all chemical shifts are reported in parts per million (ppm, δ). EIMS and HREIMS spectra were obtained on a VG-70-250S mass spectrometer. Elemental analyses were determined by Elementer Vario EL III and gave combustion values for C, H, N, and S within 0.4% of the theoretical values. Column chromatography was performed on silica gel (70–230 mesh, 230–400 mesh). TLC was conducted on precoated Kieselgel 60 F254 plates (Merck), and the spots were detected by UV. Concentration of the reaction solutions involved the use of rotary evaporator under reduced pressure.

5.1.1. General procedure for the synthesis of 2a, 3a, 4a, and 5a

To a solution of 2,4-dihdroxyacetophenone (**1**) in acetone (100 mL) was added freshly ignited K_2CO_3 (6.0 g) followed by ethyl iodide, methyl iodide, isopropyl bromide, or prenyl bromide at room temperature. Each reaction mixture was separately refluxed for 8 h at 80 °C. The progress of the reaction was monitored by TLC. On completion of the reaction, the solvent was removed by filtration and evaporated under reduced pressure and the residue was purified by column chromatography (hexanes and EtOAc mixtures) to yield the title compounds **2a**, **3a**, **4a**, and **5a**, respectively.

Table 1
Cytotoxic activity data for compounds **9–47**

Compound	EC_{50} (μg/mL)			
	PC-3	MCF-7	KB	KB-VIN
9	0.95	0.08	1.54	0.80
10	10.52	0.25	3.41	1.13
11	2.80	0.66	5.12	1.45
12	NA[a]	3.19	8.43	7.21
13	NA	10.61	NA	NA
14	NA	20.00	NA	NA
15	NA	NA	NA	NA
16	3.14	4.13	5.72	5.55
17	6.72	5.24	NA	9.92
18	NA	NA	NA	NA
19	0.84	0.10	NA	4.64
20	0.78	0.03	14.90	3.50
21	8.11	2.74	9.60	6.58
22	6.60	3.12	7.75	6.25
23	16.79	1.51	13.54	8.12
24	4.04	0.24	9.44	5.02
25	0.31	0.12	0.73	0.30
26	0.68	0.29	2.11	0.69
27	0.10	0.15	0.74	0.41
28	0.18	0.15	2.11	0.69
29	7.43	4.87	6.12	3.27
30	6.49	5.62	5.14	2.58
31	11.79	4.80	NA	11.45
32	6.61	5.67	5.93	3.29
33	1.72	1.34	2.31	2.27
34	12.09	16.22	9.92	11.99
35	0.83	0.43	1.30	0.68
36	0.90	0.67	2.17	1.17
37	1.87	1.23	1.95	2.62
38	3.80	4.70	5.63	5.77
39	1.09	1.66	2.84	2.15
40	2.73	1.12	5.70	1.64
41	0.33	0.28	0.83	0.36
42	0.44	0.46	0.82	0.71
43	0.66	0.42	1.12	0.60
45	2.02	0.11	2.93	2.09
46	3.07	0.47	5.18	2.61
47	6.77	0.30	6.14	2.64

[a] Not active.

5.1.2. 1-(4-Ethoxy-2-hydroxyphenyl)ethanone (2a)

Compound **1** (15.2 g, 0.1 mol) and ethyl iodide (8 mL) were treated as described above. The crude product was purified by column chromatography eluting with hexanes/EtOAc (8:2) to yield **2a** as a colorless crystalline solid (17.5 g, 97%), mp 46–47 °C. IR (neat) 2983, 1635, 1506, 1476, 1426, 1371, 1331, 1255, 1037, 987, 803 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 12.71 (1H, s, OH), 7.58 (1H, d, J = 8.7 Hz), 6.40 (1H, d, J = 1.8 Hz) 6.38 (1H, dd, J = 8.7, 1.8 Hz), 4.02 (2H, m), 2.51 (3H, s), 1.39 (3H, t, J = 4.0 Hz). EIMS, *m/z* (% rel. intensity): 180 (67) $[M]^+$, 166 (12), 165 (100), 164 (13), 137 (93), 86 (20), 43 (34).

5.1.3. 1-(2-Hydroxy-4-methoxyphenyl)ethanone (3a)

Compound **1** (15.2 g, 0.1 mol) and methyl iodide (7 mL) were treated as described above. The crude product was purified by column chromatography eluting with hexanes/EtOAc (9:1) to yield **3a** as a colorless crystalline solid (15.8 g, 95%), mp 52–53 °C. IR (neat) 2972, 2875, 1637, 1500, 1442, 1369, 1332, 1274, 1208, 1156, 1109, 1065, 1025, 956, 897 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 12.70 (1H, s, OH), 7.56 (1H, d, J = 9.0 Hz), 6.37 (2H, m), 3.78 (3H, s), 2.50 (3H, s). EIMS, *m/z* (% rel. intensity): 166 (48) $[M]^+$, 151 (100), 123 (22), 108 (10), 100 (5), 77 (9), 65 (8) 43 (18).

5.1.4. 1-(2-Hydroxy-4-isopropoxyphenyl)ethanone (4a)

Compound **1** (7.6 g, 0.05 mol) and isopropyl bromide (5 mL) were treated as described above. The crude product was purified by column chromatography eluting with hexanes/$CHCl_3$ (1:1) to yield **4a** as a yellow syrup (7.6 g, 76%). IR (neat) 2980, 1633, 1583, 1426, 1371, 1330, 1273, 1256, 1175, 1136, 1066, 923, 834, 804 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 12.68 (1H, s, OH), 7.52 (1H, d, J = 9.0 Hz), 6.32 (2H, br s), 4.52 (1H, m), 2.45 (3H, s), 1.29 (6H, d, J = 6.0 Hz). EIMS, *m/z* (% rel. intensity): 194 (23) $[M]^+$, 152 (17), 137 (100), 123 (2), 105 (1), 77 (2), 43 (9).

5.1.5. 1-[2-Hydroxy-4-(3-methylbut-2-enyloxy)phenyl]ethanone (5a)

Compound **1** (7.6 g, 0.05 mol) and prenyl bromide (6 mL) were treated as described above. The crude product was purified by column chromatography eluting with hexanes/EtOAc (9:1) to yield **5a** as a colorless crystalline solid (9.0 g, 82%), mp 42–43 °C. IR (neat) 2975, 2933, 1633, 1505, 1330, 1273, 1252, 1191, 1151, 1136, 1066, 952, 834 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 12.72 (1H, s, OH), 7.60 (1H d, J = 9.0 Hz), 6.44 (1H, dd, J = 9.0, 2.0 Hz), 6.41 (1H, d, J = 2.0 Hz). 5.45 (1H, t, J = 6.0 Hz), 4.52 (2H, d, J = 6.0 Hz), 2.53 (3H, s), 1.78 (3H, s), 1.73 (3H, s). EIMS, *m/z* (% rel. intensity): 220 (2) $[M]^+$, 194 (22), 152 (24), 137 (100), 69 (7), 43 (9).

5.2. General procedure for the synthesis of Mannich bases of acetophenones and aldehydes

To a solution of hydroxyl-substituted acetophenone or aldehyde and formaldehyde (37% solution) in EtOH (75 mL) was added the corresponding secondary amine (morpholine or piperidine) at room temperature as reported in earlier literature.[23,27–29] Then, the resulting mixture was heated to reflux for 18–22 h at 120 °C. On completion, the reaction mixture was concentrated under reduced pressure and the crude product was purified by column chromatography to yield a mixture of *ortho*- and *para*-substituted Mannich bases of acetophenones.

5.2.1. 1-[2,4-Dihydroxy-3-(morpholinomethyl)phenyl]ethanone (1a)

Compound **1** (3.8 g, 0.025 mol), formaldehyde (2.1 mL, 0.025 mol), and morpholine (2.2 mL, 0.025 mol) were treated as described above. The crude product was purified by column chromatography eluting with hexanes/EtOAc (6:4) to yield **1a** as colorless needles (4.2 g, 67%), mp 116–117 °C. IR (neat) 3016, 2949, 1612, 1494, 1445, 1307, 1270, 1215, 1169, 1118, 1066, 992, 905, 854, 759, 663, 628 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 13.13 (1H, s, OH), 8.85 (1H, s, OH), 7.56 (1H, d, J = 9.0 Hz), 6.34 (1H, d, J = 9.0 Hz), 3.85 (2H, s), 3.76 (4H, s), 2.75 (4H, s), 2.57 (3H, s). EIMS, m/*z* (% rel. intensity): 251 (76) $[M]^+$, 222 (14), 206 (13), 204 (13), 193 (79), 178 (19), 166 (12), 165 (67), 164 (41), 149 (24), 147 (29), 86 (100), 65 (13), 57 (33), 43 (23).

5.2.2. 1-[4-Ethoxy-2-hydroxy-5-(morpholinomethyl)phenyl]-ethanone (2b) and 1-[4-ethoxy-2-hydroxy-3-(morpholinomethyl)-phenyl]ethanone (2c)

Compound **2a** (10.0 g, 0.056 mol), formaldehyde (4.6 mL, 0.056 mol), and morpholine (5.0 mL, 0.056 mol) were treated as described above. The crude product was purified by column chromatography eluting with hexanes/EtOAc (1:1) to yield **2b** (13.0 g, 83%) and **2c** (900 mg, 6%). **2b**: colorless solid, mp 127–128 °C. IR (neat) 2957, 2852, 1633, 1497, 1475, 1453, 1371, 1333, 1270, 1233, 1193, 1153, 1115, 1085, 1004, 906, 865 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 12.68 (1H, s), 7.65 (1H, s), 6.33 (1H, s), 4.09 (2H, m), 3.65 (4H, m), 3.43 (2H, s), 2.58 (4H, s), 2.45 (3H, s), 1.41 (3H, t, J = 6.0 Hz). EIMS, *m/z* (% rel. intensity): 279 (11) $[M]^+$, 221 (16), 194 (14), 193 (91), 165 (42), 149 (15), 147 (13), 137 (25), 100 (100), 86 (38), 56 (42). **2c**: colorless oil. IR (neat) 2937, 2845, 1624, 1485, 1472, 1370, 1333, 1271, 1228, 1080, 907, 865 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.66 (1H, d, J = 9.0 Hz), 6.41 (H, d, J = 9.0 Hz), 4.07 (2H, m), 3.65 (4H, m), 2.86 (2H, s), 2.53 (4H, s),

2.44 (3H, s), 1.40 (3H, t, J = 6.0 Hz). EIMS, *m/z* (% rel. intensity): 279 (27) $[M]^+$, 264 (6), 221 (19), 206 (4), 186 (3), 165 (43), 149 (15), 100 (100), 86 (39), 42 (6).

5.2.3. 1-[2-Hydroxy-4-methoxy-5-(morpholinomethyl)phenyl]-ethanone (3b) and 1-[2-hydroxy-4-methoxy-3-(morpholinomethyl)phenyl]ethanone (3c)

Compound **3a** (10.0 g, 0.06 mol), formaldehyde (4.9 mL, 0.06 mol), and morpholine (5.2 mL, 0.06 mol) were treated as described above. The crude product was purified by column chromatography eluting with hexanes/EtOAc (6:4) to yield **3b** (13.6 g, 86%) and **3c** (810 mg, 5%). **3b**: colorless solid, mp 130–131 °C. IR (neat) 2947, 2848, 1625, 1499, 1453, 1418, 1273, 1237, 1157, 1115, 1093, 1029, 895, 793 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 12.35 (1H, s, OH), 7.64 (1H, s), 6.42 (1H, s), 3.85 (5H, s), 3.65 (4H, m), 2.52 (7H, m). EIMS, *m/z* (% rel. intensity): 265 (42) $[M]^+$, 236 (11), 220 (12), 207 (46), 192 (10), 179 (100), 86 (68), 43 (15). **3c**: colorless oil. IR (neat) 2845, 1620, 1499, 1445, 1368, 1307, 1270, 1169, 992, 807, 759 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 12.31 (1H, s, OH), 7.67 (1H, d, J = 9.0 Hz), 6.44 (1H, d, J = 9.0 Hz), 3.85 (5H, s), 3.65 (4H, m), 2.52 (7H, m). EIMS, *m/z* (% rel. intensity): 265 (38) $[M]^+$, 264 (3), 220 (24), 179 (100), 165 (13), 163 (18), 149 (22), 86 (56), 43 (14).

5.2.4. 1-[2-Hydroxy-4-isopropoxy-3-(morpholinomethyl)phenyl]-ethanone (4b) and 1-[2-hydroxy-4-isopropoxy-5-(morpholinomethyl)phenyl]ethanone (4c)

Compound **4a** (5.0 g, 0.026 mol), formaldehyde (2.1 mL, 0.026 mol), and morpholine (2.3 mL, 0.026 mol) were treated as described above. The crude product was purified by column chromatography eluting with hexanes/EtOAc (7:3) to yield **4b** (725 mg, 10%) and **4c** (4.8 g, 66%). **4b**: pale yellow oil. IR (neat) 2958, 1630, 1560, 1428, 1367, 1252, 1168, 1112, 941, 837 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 12.70 (1H, s, OH), 7.66 (1H, d, J = 9.0 Hz), 6.45 (1H, d, J = 9.0 Hz), 4.68 (1H, m), 3.70 (6H, m), 2.56 (7H, s), 1.35 (6H, d, J = 6.0 Hz); EIMS, *m/z* (% rel. intensity): 293 (100) $[M]^+$, 275 (17), 241 (2), 100 (15), 86 (19). **4c**: Colorless oil. IR (neat) 2852, 1628, 1468, 1418, 1367, 1165, 1110, 938 cm^{-1}. ^1H NMR ($CDCl_3$,300 MHz): δ 12.68 (1H, s, OH), 7.69 (1H, s), 6.36 (1H, s), 4.64 (1H, m), 3.69 (6H, m), 2.56 (7H, m), 1.33 (6H, d, J = 6.0 Hz). EIMS, *m/z* (% rel. intensity): 293 (32) $[M]^+$, 149 (100), 110 (17), 86 (54).

5.2.5. 1-[2-Hydroxy-4-(3-methylbut-2-enyloxy)-3-(morpholinomethyl)phenyl]ethanone (5b)

Compound **5a** (4.0 g, 0.018 mol), formaldehyde (1.5 mL, 0.018 mol), and morpholine (1.6 mL, 0.018 mol) were treated as described above. The crude product was purified by column chromatography eluting with hexanes/EtOAc (7:3) to yield **5b** as a colorless solid (5.0 g, 86%), mp 64–65 °C. IR (neat) 2954, 2853, 2808, 1630, 1495, 1452, 1418, 1369, 1270, 1162, 1116, 1080, 1004, 978, 864 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.68 (1H, d, J = 9.0 Hz), 6.46 (1H, d, J = 9.0 Hz), 5.44 (1H, t, J = 6.0 Hz), 4.59 (2H, d, J = 6.0 Hz), 3.72 (6H, s), 2.58 (7H, s), 1.79 (3H, s), 1.74 (3H, s). EIMS, *m/z* (% rel. intensity): 319 (41) $[M]^+$, 251 (8), 250 (30), 233 (10), 217 (13), 192 (15), 179 (6), 165 (100), 147 (15), 137 (19), 86 (67), 69 (40), 56 (11).

5.2.6. 1-[4-Hydroxy-3-(morpholinomethyl)phenyl]ethanone (6a)

Compound **6** (13.6 g, 0.1 mol), formaldehyde (8.2 mL, 0.1 mol), and morpholine (8.7 mL, 0.1 mol) were treated as described above. The crude product was purified by column chromatography eluting with hexanes/EtOAc (8:2) to yield **6a** as a colorless solid (19.0 g, 81%). 67–68 °C. IR (neat) 2961, 2851, 1673, 1592, 1497, 1453, 1358, 1292, 1245, 1174, 1073, 1030, 964, 893, 862, 769 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.80 (1H, dd, J = 2.2, 9.0 Hz), 7.66 (1H, d, J = 2.2 Hz), 6.83 (1H, d, J = 8.6 Hz), 3.62 (6H, m), 2.48 (4H, m), 2.39 (3H, s). EIMS, *m/z* (% rel. intensity): 235 (100) $[M]^+$, 204 (16), 190 (5), 188 (35), 176 (11), 162 (18), 149 (76), 134 (11), 133 (15), 106 (9), 86 (38), 77 (16), 57 (19), 56 (18), 43 (17).

5.2.7. 1-[4-Hydroxy-3,5-bis(morpholinomethyl)phenyl]ethanone (6b)

Compound **6** (3.4 g, 0.025 mol), formaldehyde (4.1 mL, 0.05 mol), and morpholine (4.3 mL, 0.05 mol) were treated as described above. The crude product was purified by column chromatography eluting with EtOAc/MeOH (9:1) to yield **6b** as a colorless solid (5.0 g, 60%), mp 71–72 °C. IR (neat) 2957, 2851, 1677, 1599, 1474, 1412, 1357, 1306, 1245, 1115, 1071, 1032, 904, 864, 803 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.69 (2H, s), 3.71 (8H, m), 3.63 (4H, s), 2.54 (11H, m). EIMS, *m/z* (% rel. intensity): 334 (4) $[M]^+$, 249 (5), 248 (6), 247 (13), 217 (3), 133 (6), 100 (100), 70 (4), 56 (15), 43 (5).

5.2.8. 1-[3-Hydroxy-4-(morpholinomethyl)phenyl]ethanone (7a), 1-[3-hydroxy-2-(morpholinomethyl)phenyl]ethanone (7b) and 1-[3-hydroxy-2,4-bis(morpholinomethyl)phenyl]ethanone (7c)

Compound **7** (13.6 g, 0.1 mol), formaldehyde (8.2 mL, 0.1 mol), and morpholine (8.7 mL, 0.1 mol) were treated as described in Section 5.2. The crude product was purified by column chromatography eluting with hexanes/$CHCl_3$ (1:1) to yield **7a** (8.7 g, 37%) and **7c** (2.35 g, 7%). **7a**: colorless oil. IR (neat) 2961, 1652, 1583, 1471, 1349, 1291, 1242, 1070, 1028, 960, 891, 859, 826 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.32 (1H, d, J = 1.2 Hz), 7.29 (1H, d, J = 8.0 Hz), 7.01 (1H, d, J = 8.0 Hz), 3.64 (6H, m), 2.47 (7H, m). EIMS, m/*z* (% rel. intensity): 235 (24) $[M]^+$, 217 (14), 207 (31), 188 (17), 149 (100), 100 (18), 86 (21), 78 (17). **7b**: pale yellow oil, (7.2 g, 31%). IR (neat) 2965, 1648, 1572, 1469, 1240, 1068, 952, 886, 813 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.18 (1H, d, J = 8.0 Hz), 7.10 (1H, dd, J = 8.0, 2.0 Hz), 6.92 (1H, dd, J = 8.0, 2.0 Hz), 3.67 (6H, m), 2.51 (7H, m); EIMS, *m/z* (% rel. intensity): 235 (20) $[M]^+$, 149 (100), 100 (22), 86 (14). **7c**: colorless oil. IR (neat) 2948, 1647, 1613, 1568, 1413, 1239, 1020, 958, 823 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ7.15 (1H, d, J = 9.0 Hz), 6.96 (1H, d, J = 9.0 Hz), 3.98 (2H, s), 3.73 (4H, m), 3.67 (4H, m), 3.66 (2H, s), 2.55 (11H, m). EIMS, *m/z* (% rel. intensity): 334 (32) $[M]^+$, 247 (12), 189 (7) 133 (12), 100 (100), 86 (9), 56 (16).

5.2.9. 3-Hydroxy-4-methoxy-2-(piperidin-1-ylmethyl)benzaldehyde (8a)

Compound **8** (7.6 g, 0.05 mol), formaldehyde (4.1 mL, 0.05 mol), and piperidine (4.9 mL, 0.05 mol) were treated as described above. The crude product was purified by column chromatography eluting with hexanes/$CHCl_3$ (1:1) to yield **8a** as a crystalline solid (10.2 g, 82%), mp 78–79 °C. IR (neat) 2938, 2853, 1683, 1572, 1476, 1440, 1268, 1203, 1080, 1040, 987, 931, 859, 786 cm^{-1}. ^1H NMR ($CDCl_3$,300 MHz): δ 11.86 (1H, s, OH), 9.85 (1H, s, CHO), 7.23 (1H, d, J = 8.4 Hz), 6.90 (1H, d, J = 8.4 Hz), 4.34 (2H, s), 3.95 (3H, s), 2.59 (4H, s), 1.66 (4H, m), 1.50 (2H, s). EIMS, *m/z* (% rel. intensity): 249 (21) $[M]^+$, 248 (4), 221 (15), 206 (7), 178 (4), 165 (16), 164 (43), 149 (10), 84 (100), 65 (9).

5.2.10. 3-Hydroxy-4-methoxy-2-(morpholinomethyl)benzaldehyde (8b)

Compound **8** (7.6 g, 0.05 mol), formaldehyde (4.1 mL, 0.05 mol) and morpholine (4.3 mL, 0.05 mol) were treated as described above. The crude product was purified by column chromatography eluting with hexanes/$CHCl_3$ (1:1) to yield **8b** as a crystalline solid (10.8 g, 86%), 81–82 °C. IR (neat) 2960, 2848, 1690, 1600, 1571, 1466, 1443, 1302, 1264, 1209, 1115, 1073, 1030, 937, 865, 803 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 9.81 (1H, s, CHO), 9.21 (1H, s, OH), 7.22 (1H, d, J = 8.4 Hz), 6.87 (1H, d, J = 8.4 Hz), 4.33 (2H, s), 3.90 (3H, s), 3.68 (4H, s), 2.58 (4H, s). EIMS, *m/z* (% rel. intensity): 252 (14) $[M]^+$,

223 (13), 193 (3), 192 (7), 178 (3), 166 (9), 165 (26), 164 (100), 149 (15), 137 (10), 136 (24), 135 (16), 86 (13).

5.3. General procedure for the synthesis of Mannich bases of chalcones

The general synthetic strategy employed to prepare the Mannich bases of heterocyclic chalcone derivatives was based on the Claisen–Schmidt condensation. As shown in Scheme 2, a series of 39 Mannich bases of heterocyclic chalcones (**9–47**) were prepared by base-catalyzed condensation of substituted Mannich bases of acetophenones with appropriate heterocyclic aldehydes in MeOH. To a stirred reaction mixture at 0 °C was added a 30% solution of KOH (40 mL) dropwise over 30 min. The reaction mixture was kept at room temperature for 24 h, then diluted with water and extracted with EtOAc. Pure target compounds were obtained by silica gel column chromatography (cc) of the residue eluting with various solvent mixtures as indicated below. The structures of all the 39 Mannich bases of heterocyclic chalcones were established on the basis of IR, ^{1}H, ^{13}C NMR, EIMS, HREIMS, and elemental analyses.

5.3.1. (*E*)-1-[2,4-Dihydroxy-3-(morpholinomethyl)phenyl]-3-(pyridin-2-yl)prop-2-en-1-one (9)

Compound **1a** (1.0 g, 3.77 mmol) and 2-pyridinecarboxaldehyde (405 mg, 3.78 mmol) were treated as described above. The crude product was purified by cc eluting with diisopropylether/MeOH (7:3) to yield **9** as a yellow crystalline solid (850 mg, 64%), mp 176–177 °C. IR (neat) 2960, 2902, 1639, 1610, 1576, 1487, 1401, 1356, 1290, 1249, 1224, 1117, 907, 786, 595 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 13.70 (1H, s, OH), 8.84 (1H, s, OH), 8.68 (1H, d, J = 4.2 Hz), 8.17 (1H, d, J = 15.0 Hz), 7.88 (1H, d, J = 9.0 Hz), 7.79 (1H, d, J = 15.0 Hz), 7.75 (1H, d, J = 7.5 Hz), 7.45 (1H, d, J = 7.5 Hz), 7.27 (1H, d, J = 4.2 Hz), 6.40 (1H, d, J = 9.0 Hz), 3.89 (2H, s), 3.77 (4H, s), 2.64 (4H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 191.8, 166.3, 164.1, 153.0, 150.1, 141.8, 136.8, 131.3, 125.5, 124.3, 124.3, 113.0, 108.6, 106.7, 66.5 (2×), 53.7, 52.8 (2×). EIMS, *m/z* (% rel. intensity): 340 (36) [M]$^+$, 322 (9), 273 (7), 255 (100), 237 (22), 226 (12), 207 (33), 196 (9), 177 (8), 149 (21), 132 (33), 106 (34), 86 (16). HREIMS *m/z* calcd for $C_{19}H_{20}N_2O_4$, 340.1423; found, 340.1422. Elemental analysis: calcd C, 67.05; H, 5.92; N, 8.23; found, C, 66.73; H, 6.01; N, 8.14.

5.3.2. (*E*)-1-[2-Hydroxy-4-methoxy-3-(morpholinomethyl)phenyl]-3-(pyridin-2-yl)prop-2-en-1-one (10)

Compound **3c** (1.0 g, 3.78 mmol) and 2-pyridinecarboxaldehyde (403 mg, 3.76 mmol) were treated as described above. The crude product was purified by cc eluting with hexanes/EtOAc (7:3) to yield **10** (yellow solid, 750 mg, 56%), mp 161–162 °C. IR (neat) 2948, 1639, 1582, 1495, 1432, 1352, 1318, 1288, 1232, 1113, 1074, 978, 863 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.69 (1H, d, J = 4.5 Hz), 8.24 (1H, d, J = 15.3 Hz), 8.11 (1H, d, J = 9.0 Hz), 7.94 (1H, d, J = 8.7 Hz), 7.90 (1H, s), 7.77 (1H, d, J = 15.3 Hz), 7.44 (1H, dd, J = 4.5, 8.7 Hz), 3.89 (3H, s), 3.85 (2H, s), 3.53 (4H, t, J = 4.2 Hz), 2.43 (4H, t, J = 4.2 Hz). ^{13}C NMR (DMSO-d_6, 75 MHz): δ194.8, 165.5, 164.2, 153.6, 150.2, 143.2, 136.6, 131.3, 125.5, 124.3, 124.2, 114.3, 108.6, 106.6, 66.5 (2×), 58.9, 53.8, 52.8 (2×). EIMS, *m/z* (% rel. intensity): 354 (40), [M]$^+$, 336 (11), 297 (12), 270 (20), 269 (100), 268 (35), 251 (26), 221 (51), 163 (30), 133 (19), 132 (59), 106 (29), 98 (18). HREIMS *m/z* calcd for $C_{20}H_{22}N_2O_4$, 354.1580; found, 354.1581. Elemental analysis: calcd C, 67.78; H, 6.26; N, 7.90; found, C, 67.58; H, 6.25; N, 7.87.

5.3.3. (*E*)-1-[2-Hydroxy-4-isopropoxy-3-(morpholinomethyl)phenyl]-3-(thiophen-2-yl)prop-2-en-1-one (11)

Compound **4C** (1.0 g, 3.41 mmol) and 2-thiophenecarboxaldehyde (400 mg, 3.57 mmol) were treated as described above. The crude product was purified by cc eluting with diisopropyl ether/MeOH (8:2) to yield **11** (yellow crystalline solid, 720 mg, 55%), mp 97–98 °C. IR (neat) 2850, 1627, 1490, 1420, 1275, 1247, 1112, 1058, 1003, 966, 862, 793, 705 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.09 (1H, d, J = 9.0 Hz), 7.96 (1H, d, J = 15.3 Hz), 7.80 (1H, d, J = 6.0 Hz), 7.69 (1H, d, J = 3.6 Hz), 7.65 (1H, d, J = 15.3 Hz), 7.19 (1H, dd, J = 3.6, 6.0 Hz), 6.68 (1H, d, J = 9.0 Hz), 4.78 (1H, m), 3.50 (6H, m), 2.41 (4H, m),1.29 (6H, d, J = 6.0 Hz). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 191.1, 163.3, 162.4, 139.7, 136.3, 132.9, 131.7, 130.8, 128.7, 120.1, 114.1, 112.4, 104.4, 70.3, 66.2 (2×), 53.0 (2×), 49.4, 21.8 (2×). EIMS, *m/z* (% rel. intensity): 387 (59) [M]$^+$, 358 (5), 329 (20), 302 (21), 293 (9), 259 (17), 244 (58), 205 (12), 191 (14), 165 (23), 149 (100), 147 (12), 110 (17), 86 (54), 71 (32), 57 (43). HREIMS *m/z* calcd for $C_{21}H_{25}NO_4S$, 387.1504; found, 387.1504. Elemental analysis: calcd C, 65.09; H, 6.50; N, 3.61; S, 8.27; found, C, 65.06; H, 6.48; N, 3.61; S, 8.39.

5.3.4. (*E*)-1-[2-Hydroxy-4-(3-methylbut-2-enyloxy)-3-(morpholinomethyl)phenyl]-3-(3-methylthiophen-2-yl)prop-2-en-1-one (12)

Compound **5b** (1.0 g, 3.13 mmol) and 3-methyl-2-thiophenecarboxaldehyde (400 mg, 3.17 mmol) were treated as described above. The crude product was purified by cc eluting with diisopropylether/MeOH (7:3) to yield **12** (yellow solid, 1.1 g, 82%), mp 126–127 °C. IR (neat) 2937, 1623, 1564, 1492, 1417, 1278, 1224, 1110, 1065, 969, 858, 791 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.07 (1H, d, J = 15.0 Hz), 8.32 (1H, d, J = 9.0 Hz), 7.34 (1H, d, J = 15.0 Hz), 7.32 (1H, d, J = 5.1 Hz), 6.91 (1H, d, J = 5.1 Hz), 6.68 (1H, d, J = 9.0 Hz), 5.44 (1H, t, J = 6.6 Hz), 4.62 (2H, d, J = 6.6 Hz), 3.76 (2H, s), 3.73 (4H, s), 2.61 (4H, s), 2.41 (3H, s), 1.80 (3H, s), 1.75 (3H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 191.3, 163.9, 163.4, 142.7, 138.2, 134.8, 134.5, 131.4, 130.7, 127.3, 119.2 (2×), 115.1, 112.5, 103.1, 66.9 (2×), 65.3, 53.2 (2×), 49.8, 25.7, 18.2, 14.2. EIMS, m/*z* (% rel. intensity): 427 (52) [M]$^+$, 358 (51), 320 (9), 319 (48), 297 (7), 274 (16), 273 (77), 250 (35), 232 (17), 192 (20), 165 (61), 149 (89), 124 (23), 86 (100), 69 (62), 56 (14). HREIMS *m/z* calcd for $C_{24}H_{29}NO_4S$, 427.1817; found, 427.1815. Elemental analysis: calcd C, 67.42; H, 6.84; N, 3.28; S, 7.50; found, C, 67.41; H, 6.83; N, 3.24; S, 7.57.

5.3.5. (*E*)-1-[4-Ethoxy-2-hydroxy-5-(morpholinomethyl)phenyl]-3-(pyridin-3-yl)prop-2-en-1-one (13)

Compound **2b** (500 mg, 1.80 mmol) and 3-pyridinecarboxaldehyde (208 mg, 1.73 mmol) were treated as described above. The crude product was purified by cc eluting with diisopropyl ether/MeOH (8:2) to yield **13** (pale yellow solid, 495 mg, 75%), mp 152–153 °C. IR (neat) 2936, 1639, 1537, 1359, 1287, 1230, 1194, 1112, 1011, 980, 864, 819 cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 13.31 (1H, s, OH), 9.04 (1H, s), 8.61 (1H, t, J = 3.0 Hz), 8.35 (1H, d, J = 6 Hz), 8.12 (1H, s), 8.09 (1H, d, J = 15.0 Hz), 7.82 (1H, d, J = 15.0 Hz), 7.50 (1H, dd, J = 3.0, 6.0 Hz), 6.53 (1H, s), 4.10 (2H, q), 3.54 (4H, s), 3.44 (2H, s), 2.39 (4H, s), 1.34 (3H, t, J = 6.0 Hz). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 191.3, 165.2, 164.1, 151.1, 150.4, 140.5, 135.3, 133.2, 130.3, 123.9, 123.2, 117.5, 112.8, 99.8, 66.2 (2×), 64.0, 55.4, 52.9 (2×), 14.3. EIMS, *m/z* (% rel. intensity): 368 (23) [M]$^+$, 353 (5), 283 (35), 282 (100), 177 (28), 149 (8), 133 (8), 86 (6). HREIMS *m/z* calcd for $C_{21}H_{24}N_2O_4$, 368.1736; found, 368.1737. Elemental analysis: calcd C, 68.46; H, 6.57; N, 7.60; found, C, 68.48; H, 6.60; N, 7.60.

5.3.6. (*E*)-1-[4-Ethoxy-2-hydroxy-5-(morpholinomethyl)phenyl]-3-(furan-2-yl)prop-2-en-1-one (14)

Compound **2b** (500 mg, 1.80 mmol) and 2-furaldehyde (172 mg, 1.80 mmol) were treated as described above. The crude product was purified by cc eluting with diisopropyl ether/MeOH (9:1 to 8:2) to yield **14** (yellow crystalline solid, 580 mg, 91%), mp 157–

158 °C. IR (neat) 2820, 1639, 1574, 1550, 1353, 1276, 1232, 1114, 1010, 966, 859 cm^{-1}. ^1H NMR (DMSO-d_6,300 MHz): δ 13.29 (1H, s, OH), 7.94 (2H, s), 7.64 (1H, d, J = 15.3 Hz), 7.55 (1H, d, J = 15.3 Hz), 7.12 (1H, d, J = 3.0 Hz), 6.70 (1H, dd, J = 3.0, 3.0 Hz), 6.51 (1H, s), 4.11 (2H, q), 3.55 (4H, m), 3.43 (2H, s), 2.39 (4H, s), 1.33 (3H, t, J = 6.0 Hz). ^{13}C NMR (DMSO-d_6,75 MHz): δ 190.8, 172.9, 164.7, 163.7, 151.0, 146.5, 132.1, 130.2, 117.8, 117.6, 113.2, 112.9, 95.1, 66.2 (2×), 64.0, 55.0, 52.9 (2×), 14.3. EIMS, *m/z* (% rel. intensity): 357 (39) $[M]^+$, 342 (2), 272 (21), 271 (100), 177 (68), 149 (8), 133 (12), 121 (10), 86 (6), 69 (6). HREIMS *m/z* calcd for $C_{20}H_{23}NO_5$, 357.1576; found, 357.1579. Elemental analysis: calcd C, 67.21; H, 6.49; N, 3.92; found, C, 67.31; H, 6.48; N, 3.92.

5.3.7. (*E*)-1-[4-Ethoxy-2-hydroxy-5-(morpholinomethyl)phenyl]-3-(5-methylfuran-2-yl)prop-2-en-1-one (15)

Compound **2b** (500 mg, 1.80 mmol) and 5-methyl-2-furaldehyde (197 mg, 1.80 mmol) were treated as described above. The crude product was purified by cc eluting with diisopropyl ether/MeOH (9:1) to obtain **15** (pale yellow solid, 450 mg, 67%), mp 148–149 °C. IR (neat) 2930, 1638, 1563, 1525, 1348, 1371, 1267, 1231, 1146, 1115, 1014 cm^{-1}. ^1H NMR (DMSO-d_6,300 MHz): δ13.40 (1H, s, OH), 7.92 (1H, s), 7.57 (1H, d, J = 15.0 Hz), 7.42 (1H, d, J = 15.0 Hz), 7.02 (1H, d, J = 3.0 Hz), 6.50 (1H, s), 6.35 (1H, d, J = 3.0 Hz), 4.09 (2H, q), 3.55 (4H, m), 3.43 (2H, s), 2.39 (7H, s),1.33 (3H, t, J = 6.0 Hz). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 190.8, 164.7, 163.5, 156.5, 149.8, 131.9, 130.2, 119.7, 117.5, 115.9, 112.9, 110.0, 99.8, 66.2 (2×), 63.9, 55.0, 52.9 (2×), 14.3, 13.7. EIMS, *m/z* (% rel. intensity): 371 (38) $[M]^+$, 286 (22), 285 (100), 284 (15), 177 (52), 149 (7), 133 (13), 121 (12), 107 (6), 77 (6), 56 (9). HREIMS *m/z* calcd for $C_{21}H_{25}NO_5$, 371.1733; found, 371.1735. Elemental analysis: calcd C, 67.91; H, 6.78; N, 3.77; found, C, 67.86; H, 6.77; N, 3.79.

5.3.8. (*E*)-1-[4-Ethoxy-2-hydroxy-5-(morpholinomethyl)phenyl]-3-(pyridin-2-yl)prop-2-en-1-one (16)

Compound **2b** (500 mg, 1.80 mmol) and 2-pyridinecarboxaldehyde (191 mg, 1.78 mmol) were treated as described above. The crude product was purified by cc eluting with diisopropyl ether/MeOH (8:2) to yield **16** (pale yellow solid, 365 mg, 55%), mp 154–155 °C. IR (neat) 2933, 1643, 1580, 1497, 1433, 1358, 1286, 1230, 1114, 1037, 1010, 976, 864, 818 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 13.14 (1H, s, OH), 8.69 (1H, d, J = 3.0 Hz), 8.18 (1H, d, J = 15.0 Hz), 7.98 (1H, s), 7.89 (2H, t, J = 3.0 Hz), 7.77 (1H, d, J = 15.0 Hz), 7.43 (1H, dd, J = 3.0, 3.0 Hz), 6.54 (1H, s), 4.11 (2H, q), 3.55 (4H, m), 3.43 (2H, s), 2.39 (4H, s), 1.34 (3H, t, J = 6.0 Hz). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 191.5, 164.8, 163.9, 152.5, 150.1, 142.6, 137.2, 132.4, 125.4 (2×), 124.9, 124.4, 113.1, 99.8, 66.2 (2×), 64.0, 55.0, 52.9 (2×), 14.3. EIMS, *m/z* (% rel. intensity): 368 (13) $[M]^+$, 326 (12), 294 (9), 283 (72), 282 (100), 268 (24), 239 (12), 210 (6), 177 (21), 149 (14), 132 (15), 106 (18), 78 (8), 57 (9). HREIMS *m/z* calcd for $C_{21}H_{24}N_2O_4$, 368.1736; found, 368.1735. Elemental analysis: calcd C, 68.46; H, 6.57; N, 7.60; found, C, 68.14; H, 6.63; N, 7.49.

5.3.9. (*E*)-1-[4-Ethoxy-2-hydroxy-5-(morpholinomethyl)phenyl]-3-phenylprop-2-en-1-one (17)

Compound **2b** (500 mg, 1.80 mmol) and benzaldehyde (190 mg, 1.80 mmol) were treated as described above. The crude product was purified by cc eluting with diisopropyl ether/MeOH (9.5:0.5) to yield **17** (pale yellow solid, 425 mg, 65%), mp 160–161 °C. IR (neat) 2981, 1639, 1573, 1496, 1449, 1360, 1279, 1230, 1193, 1115, 1035, 864, 731 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 13.40 (1H, s, OH), 8.11 (1H, s), 7.94 (1H, d, J = 15.0 Hz), 7.89 (2H, m), 7.80 (1H, d, J = 15.0 Hz), 7.46 (3H, m), 6.52 (1H, s), 4.09 (2H, q), 3.53 (4H, m), 3.44 (2H, s), 2.39 (4H, s), 1.33 (3H, t, J = 6.9 Hz). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 191.7, 165.1, 163.9, 143.9, 134.5, 133.0, 130.7, 129.0 (2×), 128.9 (2×), 121.2, 117.4, 112.8, 99.8, 66.2 (2×), 64.0, 55.3, 52.9 (2×), 14.3. EIMS, *m/z* (% rel. intensity): 367 (63) $[M]^+$, 352 (5), 282 (34), 281 (100), 203 (6), 177 (70), 149 (9), 133 (13), 126 (10), 86 (9). HREIMS *m/z* calcd for $C_{22}H_{25}NO_4$, 367.1784; found, 367.1786. Elemental analysis: calcd C, 71.91; H, 6.86; N, 3.81; found, C, 71.93; H, 6.89; N, 3.76.

5.3.10. (*E*)-1-[4-Ethoxy-2-hydroxy-5-(morpholinomethyl)phenyl]-3-(3-methylthiophen-2-yl)prop-2-en-1-one (18)

Compound **2b** (500 mg, 1.80 mmol) and 3-methyl-2-thiophenecaroxaldehyde (225 mg, 1.78 mmol) were treated as described above. The crude product was purified by cc eluting with diisopropyl ether/MeOH (9.5:0.5) to yield **18** (pale yellow solid, 550 mg, 79%), mp 160–161 °C. IR (neat) 2848, 1630, 1559, 1494, 1469, 1273, 1148, 1114, 966, 847 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 13.28 (1H, s, OH), 7.92 (1H, s), 7.97 (1H, d, J = 15.0 Hz), 7.71 (1H, d, J = 5.0 Hz), 7.41 (1H, d, J = 15.0 Hz), 7.04 (1H, d, J = 5.0 Hz), 6.51 (1H, s), 4.09 (2H, q), 3.57 (4H, s), 3.43 (2H, s), 2.40 (4H, s), 2.37 (3H, s), 1.34 (3H, t, J = 6.0 Hz). ^{13}C NMR (DMSO-d_6,75 MHz): δ 190.7, 164.6, 163.5, 143.3, 134.6, 133.6, 131.6, 129.3, 118.5, 117.5, 112.8, 99.8, 66.3 (2×), 64.0, 55.0, 53.0 (2×), 14.3, 13.9. EIMS, *m/z* (% rel. intensity): 387 (39) $[M]^+$, 302 (23), 301 (100), 235 (8), 177 (64), 149 (6), 133 (12), 126 (7), 98 (7). HREIMS *m/z* calcd for $C_{21}H_{25}NO_4S$, 387.1504; found, 387.1501. Elemental analysis: calcd C, 65.09; H, 6.50; N, 3.61; S, 8.27; found, C, 65.03; H, 6.47; N, 3.54; S, 8.45.

5.3.11. (*E*)-1-[2-Hydroxy-4-methoxy-5-(morpholinomethyl)phenyl]-3-(pyridin-3-yl)prop-2-en-1-one (19)

Compound **3b** (1.0 g, 3.78 mmol) and 3-pyridinecarboxaldehyde (425 mg, 3.97 mmol) were treated as described above. The crude product was purified by cc eluting with hexanes/EtOAc (7:3) to yield **19** (yellow solid, 1.15 g, 86%), mp 144–145 °C. IR (neat) 2944, 1640, 1574, 1496, 1362, 1285, 1226, 1147, 1114, 991, 863, 831 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 13.29 (1H, s, OH), 9.04 (1H, s), 8.62 (1H, d, J = 3.0 Hz), 8.35 (1H, d, J = 6.0 Hz), 8.12 (1H, s), 8.09 (1H, d, J = 15.6 Hz), 7.82 (1H, d, J = 15.6 Hz), 7.50 (1H, t, J = 6.0 Hz), 6.56 (1H, s), 3.86 (3H, s), 3.55 (4H, s), 3.36 (2H, s), 2.38 (4H, s). ^{13}C NMR (DMSO-d_6,75 MHz): δ191.4, 165.3, 164.8, 151.1, 150.4, 140.5, 135.3, 133.3, 130.3, 123.9, 123.1, 117.4, 112.9, 99.4, 66.2 (2×), 56.1, 56.1, 53.1 (2×). EIMS, *m/z* (% rel. intensity): 354 (25) $[M]^+$, 301 (7), 269 (39), 268 (100), 163 (45), 149 (6), 133 (13). HREIMS *m/z* calcd for $C_{20}H_{22}N_2O_4$, 354.1850; found, 354.1581. Elemental analysis: calcd C, 67.78; H, 6.26; N, 7.90; found, C, 67.58; H, 6.35; N, 7.91.

5.3.12. (*E*)-1-[2-Hydroxy-4-methoxy-5-(morpholinomethyl)phenyl]-3-phenylprop-2-en-1-one (20)

Compound **3b** (1.0 g, 3.78 mmol) and benzaldehyde (402 mg, 3.78 mmol) were treated as described above. The crude product was purified by cc eluting with hexanes/EtOAc (7:3 to 6:4) to yield **20** (yellow solid, 980 mg, 73%), mp 153–154 °C. IR (neat) 2953, 1637, 1571, 1495, 1448, 1361, 1278, 1147, 1115, 992, 863, 734 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 13.42 (1H, s, OH), 8.11 (1H, s), 7.95 (1H, d, J = 15.6 Hz), 7.89 (2H, m), 7.81 (1H, d,J = 15.6 Hz), 7.47 (3H, m), 6.56 (1H, s), 3.85 (3H, s), 3.55 (4H, t, J = 4.2 Hz), 3.44 (2H, s), 2.38 (4H, t, J = 4.2 Hz). ^{13}C NMR (DMSO-d_6,75 MHz): δ 191.8, 165.2, 164.6, 144.0, 134.5, 133.1, 130.8, 129.0 (2×), 128.9 (2×), 121.2, 117.3, 112.9, 99.4, 66.2 (2×), 56.0, 55.5, 53.0 (2×). EIMS, *m/z* (% rel. intensity): 353 (43) $[M]^+$, 268 (23), 267 (100), 163 (78), 133 (22), 86 (8). HREIMS *m/z* calcd for $C_{21}H_{23}NO_4$, 353.1627; found, 353.1626. Elemental analysis: calcd C, 71.37; H, 6.56; N, 3.96; found, C, 71.34; H, 6.57; N, 3.91.

5.3.13. (*E*)-1-[2-Hydroxy-4-methoxy-5-(morpholinomethyl)phenyl]-3-(4-methoxyphenyl)prop-2-en-1-one (21)

Compound **3b** (1.0 g, 3.78 mmol) and 4-methoxybenzaldehyde (517 mg, 3.80 mmol) were treated as described above. The crude

product was purified by cc eluting with hexanes/EtOAc (7:3 to 6:4) to yield **21** (yellow solid, 720 mg, 50%), mp 137–138 °C. IR (neat) 2955, 1633, 1563, 1510, 1364, 1282, 1246, 1220, 1172, 1146, 1115, 994, 832 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 13.58 (1H, s, OH), 8.09 (1H, s), 7.86 (2H, d, J = 9.0 Hz), 7.85 (2H, d, J = 15.0 Hz), 7.03 (2H, d, J = 9.0 Hz), 6.54 (1H, s), 3.85 (3H, s), 3.82 (3H, s), 3.55 (4H, s), 3.44 (2H, s), 2.39 (4H, s). ^{13}C NMR (DMSO-d_6,75 MHz): δ 191.8, 165.2, 164.5, 161.5, 144.1, 132.9, 131.0 (2×), 127.1, 118.4, 117.1, 114.4 (2×), 112.9, 99.3, 66.2 (2×), 56.0, 55.5, 55.4, 53.0 (2×). EIMS, m/z (% rel. intensity): 383 (36) $[M]^+$, 314 (8), 298 (22), 297 (100), 179 (7), 163 (88), 133 (18), 100 (17), 86 (7). HREIMS m/z calcd for $C_{22}H_{25}NO_5$, 383.1733; found, 383.1780. Elemental analysis: calcd C, 68.91; H, 6.57; N, 3.65; found, C, 68.74; H, 6.54; N, 3.46.

5.3.14. (*E*)-1-[2-Hydroxy-4-methoxy-3-(morpholinomethyl)phenyl]-3-(thiophen-2-yl)prop-2-en-1-one (22)

Compound **3b** (1.0 g, 3.78 mmol) and 2-thiophenecarboxaldehyde (425 mg, 3.79 mmol) were treated as described above. The crude product was purified by cc eluting with hexanes/EtOAc (7:3) to yield **22** (yellow solid, 1.0 g, 74%), mp 142–143 °C. IR (neat) 2961, 1631, 1565, 1496, 1374, 1275, 1215, 1114, 993, 838, 703 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 13.44 (1H, s, OH), 7.86 (1H, d, J = 15.9 Hz), 7.77 (1H, s), 7.45 (1H, d, J = 4.8 Hz), 7.39 (1H, s), 7.25 (1H, d, J = 15.9 Hz), 7.10 (1H, dd, J = 3.6, 4.8 Hz), 6.44 (1H, s), 3.94 (3H, s), 3.77 (4H, t, J = 4.5 Hz), 3.52 (2H, s), 2.88 (4H, t, J = 4.5 Hz). ^{13}C NMR ($CDCl_3$,100 MHz): δ 191.3, 165.9, 164.4, 140.3, 136.7, 132.1, 131.7, 129.1, 128.4, 119.2, 113.3, 108.2, 99.3, 66.8 (2×), 55.7, 55.6, 53.3 (2×). EIMS, m/z (% rel. intensity): 359 (52) $[M]^+$, 329 (3), 298 (4), 274 (24), 273 (100), 164 (13), 163 (86), 133 (17), 109 (7), 86 (11), 77 (6), 56 (7). HREIMS m/z calcd for $C_{19}H_{21}NO_4S$, 359.1191; found, 359.1188. Elemental analysis: calcd C, 63.49; H, 5.89; N, 3.90; S, 8.92; found, 63.51; H, 5.87; N, 3.86; S, 9.09.

5.3.15. (*E*)-3-(Furan-2-yl)-1-[2-hydroxy-4-methoxy-3-(morpholinomethyl)phenyl]prop-2-en-1-one (23)

Compound **3b** (1.0 g, 3.78 mmol) and 2-furaldehyde (402 mg, 3.74 mmol) were treated as described above. The crude product was purified by cc eluting with hexanes/EtOAc (7:3) to yield **23** (yellow solid, 800 mg, 62%), mp 156–157 °C. IR (neat) 2955, 1636, 1573, 1551, 1353, 1276, 1226, 1146, 1115, 993, 860 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 13.51 (1H, s OH), 7.91 (1H, S), 7.66 (1H, d, J = 15.0 Hz), 7.58 (1H, S), 7.52 (1H, d, J = 15.0 Hz), 6.77 (1H, s), 6.55 (1H, s), 6.46 (1H, s), 3.88 (3H, s), 3.77 (4H, s), 3.66 (2H, s), 2.56 (4H, s). ^{13}C NMR ($CDCl_3$,100 MHz): δ191.8, 166.3, 164.6, 151.9, 145.4, 132.6, 130.6, 118.1, 116.8, 113.8, 113.0, 108.0, 99.6, 66.8 (2×), 56.0, 55.8, 53.3 (2×). EIMS, m/z (% rel. intensity): 343 (50) $[M]^+$, 258 (20), 257 (100), 164 (9), 163 (83), 133 (14), 121 (4), 86 (7), 56 (5). HREIMS m/z calcd for $C_{19}H_{21}NO_5$, 343.1420; found, 343.1422. Elemental analysis: calcd C, 66.46; H, 6.16; N, 4.08; found, 66.28; H, 6.20; N, 4.00.

5.3.16. (*E*)-1-[2-Hydroxy-4-isopropoxy-5-(morpholinomethyl)-phenyl]-3-(thiophen-2-yl)prop-2-en-1-one (24)

Compound **4c** (1.0 g, 3.41 mmol) and 2-thiophenecarboxaldehyde (400 mg, 3.57 mmol) were treated as described above. The crude product was purified by cc eluting with diisopropyl ether/MeOH (8:2 to 7:3) to yield **24** (pale yellow solid, 900 mg, 68%), mp 121–122 °C. IR (neat) 2931, 1630, 1565, 1490, 1375, 1275, 1250, 1216, 1149, 1113, 943, 837, 707 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ13.28 (1H, s, OH), 7.99 (1H, s), 7.96 (1H, d, J = 15.0 Hz), 7.80 (1H, d, J = 3.0 Hz), 7.69 (1H, d, J = 3.0 Hz), 7.56 (1H, d, J = 15.0 Hz), 7.19 (1H, t, J = 3.0 Hz), 6.53 (1H, s), 4.71 (1H, m), 3.56 (6H, s), 2.40 (4H, s), 1.28 (6H, d, J = 6.0 Hz). ^{13}C NMR (DMSO-d_6,75 MHz): δ 190.8, 164.6, 162.7, 139.6, 136.5, 133.1, 132.3, 130.8, 128.8, 119.5, 118.1, 112.7, 100.4, 70.3, 66.3 (2×), 55.1, 52.9 (2×), 21.8 (2×). EIMS, m/z (% rel. intensity): 387 (48) $[M]^+$, 372 (7), 301 (100), 259 (50), 191 (17), 164 (9), 149 (95), 121 (10), 86 (13). HREIMS m/z calcd for $C_{21}H_{25}NO_4S$, 387.1504; found, 387.1506. Elemental analysis: calcd C, 65.09; H, 6.50; N, 3.61; S, 8.27; found, C, 65.10; H, 6.51; N, 3.55; S, 8.38.

5.3.17. (*E*)-1-[4-Hydroxy-3-(morpholinomethyl)phenyl]-3-(pyridin-2-yl)prop-2-en-1-one (25)

Compound **6a** (1.0 g, 4.26 mmol) and 2-pyridinecarboxaldehyde (550 mg, 5.14 mmol) were treated as described above. The crude product was purified by cc eluting with diisopropyl ether/MeOH (8:2) to yield **25** (yellow crystalline solid, 900 mg, 65%), mp 143–144 °C. IR (neat) 2962, 1659, 1612, 1585, 1496, 1469, 1431, 1408, 1347, 1276, 1214, 1116, 1071, 1029, 1005, 988, 910, 833, 782 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ8.65 (1H, d, J = 6.0 Hz), 8.09 (1H, d, J = 15.0 Hz), 7.99 (1H, dd, J = 8.7, 2.1 Hz), 7.81 (1H, d, J = 1.5 Hz), 7.72 (1H, d, J = 15.0 Hz), 7.66 (1H, d, J = 1.5 Hz), 7.42 (1H, d, J = 8.7 Hz), 7.26 (1H, ddd, J = 1.5, 1.5, 6.0 Hz), 6.87 (1H, d, J = 8.7 Hz), 3.76 (2H, s), 3.72 (4H, s), 2.56 (4H, s). ^{13}C NMR ($CDCl_3$,75 MHz): δ188.1, 162.5, 153.1, 149.9, 141.6, 136.8, 130.6, 130.1, 129.5, 125.2, 125.1, 124.1, 120.4, 116.1, 66.4 (2×), 61.1, 52.6 (2×). EIMS, m/z (% rel. intensity): 324 (21) $[M]^+$, 294 (35), 277 (13), 239 (100), 238 (38), 210 (11), 180 (9), 132 (11), 106 (9), 86 (12), 57 (8). HREIMS m/z calcd for $C_{19}H_{20}N_2O_3$, 324.1474; found, 324.1476. Elemental analysis: calcd C, 70.35; H, 6.21; N, 8.64; found, C, 70.32; H, 6.31; N, 8.66.

5.3.18. (*E*)-1-[4-Hydroxy-3-(morpholinomethyl)phenyl]-3-(pyridin-3-yl)prop-2-en-1-one (26)

Compound **6a** (1.0 g, 4.26 mmol) and 3-pyridinecarboxaldehyde (530 mg, 4.34 mmol) were treated as described above. The crude product was purified by cc eluting with diisopropyl ether/MeOH (8:2) to yield **26** (pale yellow solid, 1.0 g, 73%), mp 114–115 °C. IR (neat) 2961, 1659, 1610, 1588, 1496, 1415, 1304, 1275, 1233, 1158, 1116, 1025, 985, 910, 864, 803, 695 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 8.98 (1H, d, J = 3.0 Hz), 8.57 (1H, t, J = 3.0 Hz), 8.34 (1H, d, J = 8.1 Hz), 8.04 (1H, d, J = 2.1 Hz), 8.02 (1H, d, J = 15.6 Hz), 7.68 (1H, d, J = 15.6 Hz), 7.45 (1H, dd, J = 4.5, 8.1 Hz), 6.88 (1H, d, J = 8.1 Hz), 3.67 (2H, s), 3.59 (4H, t, J = 4.2 Hz), 2.46 (4H, t, J = 4.2 Hz). ^{13}C NMR (DMSO-d_6,75 MHz): δ 186.8, 161.8, 150.7, 150.1, 139.2, 134.9, 131.0, 130.7, 130.1, 128.7, 123.9, 123.8, 122.5, 115.4, 66.0 (2×), 58.2, 52.6 (2×). EIMS, m/z (% rel. intensity): 324 (100) $[M]^+$, 294 (13), 293 (10), 277 (32), 239 (83), 238 (55), 210 (8), 180 (10), 167 (6), 149 (8), 132 (13), 108 (21), 86 (30), 80 (17), 57 (30). HREIMS m/z calcd for $C_{19}H_{20}N_2O_3$, 324.1474; found, 324.1473. Elemental analysis: calcd C, 70.35; H, 6.21; N, 8.64; found, C, 69.70; H, 6.31; N, 8.55.

5.3.19. (*E*)-1-[4-Hydroxy-3-(morpholinomethyl)phenyl]-3-(pyridin-4-yl)prop-2-en-1-one (27)

Compound **6a** (1.0 g, 4.26 mmol) and 4-pyridinecarboxaldehyde (520 mg, 4.30 mmol) were treated as described above. The crude product was purified by cc eluting with diisopropyl ether/MeOH (8:2 to 7:3) to yield **27** (pale yellow solid, 850 mg, 62%), mp 144–145 °C. IR (neat) 2960, 1660, 1614, 1592, 1495, 1413, 1344, 1302, 1276, 1231, 1158, 1116, 986, 911, 863, 810, 753 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz:): δ8.63 (2H, d, J = 6.0 Hz), 8.09 (1H, d, J = 15.3 Hz), 8.02 (1H, d, J = 9.0 Hz), 7.99 (1H, s), 7.79 (2H, d, J = 6.0 Hz), 7.59 (1H, d, J = 15.3 Hz), 6.88 (1H, d, J = 9.0 Hz), 3.67 (2H, s), 3.59 (4H, s), 2.46 (4H, s). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 187.0, 162.0, 150.3 (2×), 142.0, 139.8, 131.1, 130.2, 128.5, 126.4, 122.6, 122.4 (2×), 115.5, 66.1 (2×), 58.1, 52.7 (2×). EIMS, m/z (% rel. intensity): 324 (100) $[M]^+$, 277 (28), 239 (22), 238 (52), 86 (18). HREIMS m/z calcd for $C_{19}H_{20}N_2O_3$, 324.1474; found, 324.1471. Elemental analysis: calcd C, 70.35; H, 6.21; N, 8.64; found, C, 70.35; H, 6.21; N, 8.64; found C, 69.05; 6.27; N, 8.62.

5.3.20. (*E*)-1-[4-Hydroxy-3-(morpholinomethyl)phenyl]-3-phenylprop-2-en-1-one (28)

Compound **6a** (1.0 g, 4.26 mmol) and benzaldehyde (520 mg, 4.38 mmol) were treated as described above. The crude product was purified by cc eluting with hexanes/EtOAc (7:3) to yield **28** (yellow solid, 940 mg, 74%), mp 124–125 °C. IR (neat) 2960, 1657, 1609, 1590, 1494, 1448, 1334, 1304, 1275, 1229, 1157, 1116, 863, 766 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.94 (1H, dd, J = 8.2, 2.1 Hz), 7.82 (1H, s), 7.80 (1H, d, J = 15.6 Hz), 7.64 (2H, m), 7.55 (1H, d, J = 15.6 Hz), 7.38 (3H, m), 6.92 (1H, d, J = 8.2 Hz), 3.83 (2H, s), 3.78 (4H, s), 2.64 (4H, s). ^{13}C NMR ($CDCl_3$,75 MHz): δ188.4, 162.3, 143.7, 134.9, 130.4, 130.2, 130.1, 129.8, 128.8 (2×), 128.2 (2×), 121.6, 120.4, 116.0, 66.4 (2×), 61.1, 52.6 (2×). EIMS, *m/z* (% rel. intensity): 323 (100) $[M]^+$, 276 (24), 238 (15), 237 (26), 235 (12), 131 (9), 103 (10), 86 (27). HREIMS *m/z* calcd for $C_{20}H_{21}NO_3$, 323.1521; found, 323.1523. Elemental analysis: calcd C, 74.28; H, 6.55; N, 4.33; found, C, 74.27; H, 6.56; N, 4.25.

5.3.21. (*E*)-3-(Furan-2-yl)-1-[4-hydroxy-3-(morpholinomethyl)-phenyl]prop-2-en-1-one (29)

Compound **6a** (1.0 g, 4.26 mmol) and 2-furaldehyde (420 mg, 4.37 mmol) were treated as described above. The crude product was purified by cc eluting with hexanes/EtOAc (7:3 to 6:4) to yield **29** (yellow solid, 1.12 g, 84%), mp 115–116 °C. IR (neat) 2960, 1656, 1606, 1552, 1498, 1496, 1275, 1233, 1214, 1116, 1016, 864, 746 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.95 (1H, d, J = 8.4 Hz), 7.82 (1H, s), 7.57 (1H, d, J = 15.3 Hz), 7.52 (1H, s), 7.45 (1H, d, J = 15.3 Hz), 6.93 (1H, d, J = 8.7 Hz), 6.70 (1H, s), 3.85 (2H, s), 3.80 (4H, s), 2.67 (4H, s). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 187.8, 162.3, 151.8, 144.6, 130.4, 130.0, 129.9, 129.8, 120.4, 119.0, 116.1, 115.7, 112.5, 66.5 (2×), 61.3, 52.7 (2×). EIMS, *m/z* (% rel. intensity): 313 (100) $[M]^+$, 266 (22), 228 (13), 227 (17), 226 (30), 133 (18), 121 (10), 100 (5), 86 (25), 57 (10). HREIMS *m/z* calcd for $C_{18}H_{19}NO_4$, 313.1314; found, 313.1313. Elemental analysis: calcd C, 68.99; H, 6.11; N, 4.47; found, C, 68.95; H, 6.08; N, 4.43.

5.3.22. (*E*)-1-[4-Hydroxy-3-(morpholinomethyl)phenyl]-3-(thiophen-2-yl)prop-2-en-1-one (30)

Compound **6a** (1.0 g, 4.26 mmol) and 2-thiophenecarboxaldehyde (480 mg, 4.29 mmol) were treated as described above. The crude product was purified by cc eluting with diisopropyl ether/MeOH (7:3) to yield **30** (yellow solid, 920 mg, 66%), mp 148–149 °C. IR (neat) 2960, 1653, 1595, 1494, 1452, 1364, 1274, 1210, 1155, 1116, 909, 862, 820, 578 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.92 (1H, d, J = 5.4 Hz), 7.88 (1H, s), 7.77 (1H, s), 7.38 (1H, d, J = 3.6 Hz), 7.34 (1H, d, J = 15.3 Hz), 7.32 (1H, d, J = 15.3 Hz), 7.06 (1H, dd, J = 8.1, 3.6 Hz), 6.90 (1H, d, J = 8.1 Hz), 3.80 (2H, s), 3.77 (4H, s), 2.61 (4H, s). ^{13}C NMR ($CDCl_3$,75 MHz): δ 187.7, 162.3, 140.4, 136.2, 131.6, 130.3, 129.9, 129.7, 128.3, 128.2, 120.4, 120.3, 116.0, 66.4 (2×), 61.2, 52.6 (2×). EIMS, *m/z* (% rel. intensity): 329 (100) $[M]^+$, 298 (5), 282 (18), 244 (12), 243 (12), 86 (11). HREIMS *m/z* calcd for $C_{19}H_{19}NO_3S$, 329.1086; found, 329.1088. Elemental analysis: calcd C, 65.63; H, 5.81; N, 4.25; S, 9.73; found, 65.62; H, 5.81; N, 4.23; S, 9.90.

5.3.23. (*E*)-1-[4-Hydroxy-3-(morpholinomethyl)phenyl]-3-(5-methylfuran-2-yl)prop-2-en-1-one (31)

Compound **6a** (1.0 g, 4.26 mmol) and 5-methyl-2-furaldehyde (470 mg, 4.27 mmol) were treated as described above. The crude product was purified by cc eluting with hexanes/EtOAc (6:4) to yield **31** (yellow solid, 980 mg, 70%), mp 72–73 °C. IR (neat) 2920, 1656, 1606, 1522, 1496, 1366, 1347, 1322, 1299, 1210, 1183, 1155, 1117, 1021, 970, 90, 864, 827 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 7.87 (2H, m), 7.43 (1H, d, J = 15.3 Hz), 7.36 (1H, d, J = 15.3 Hz), 6.92 (1H, d, J = 3.0 Hz), 6.86 (1H, d, J = 9.0 Hz), 6.30 (1H, d, J = 3.0 Hz), 3.66 (2H, s), 3.59 (4H, s), 2.45 (4H, s), 2.36 (3H, s). ^{13}C NMR (DMSO-d_6,75 MHz): δ 186.5, 161.4, 155.6, 150.0, 135.4, 130.5, 129.4, 129.0, 122.5, 118.3, 117.0, 115.4, 109.7, 66.1 (2×), 58.1, 52.7 (2×), 13.7. EIMS, *m/z* (% rel. intensity): 327 (94) $[M]^+$, 280 (15), 254 (7), 241 (25), 240 (100), 225 (30), 197 (11), 169 (12), 141 (14), 135 (19), 106 (13), 86 (20), 77 (24), 56 (14). HREIMS *m/z* calcd for $C_{19}H_{21}NO_4$, 327.1471; found, 327.1472. Elemental analysis: calcd C, 69.71; H, 6.47; N, 4.28; found, C, 69.61; H, 6.60; N, 4.11.

5.3.24. (*E*)-1-[4-Hydroxy-3-(morpholinomethyl)phenyl]-3-(3-methylthiophen-2-yl)prop-2-en-1-one (32)

Compound **6a** (1.0 g, 4.26 mmol) and 3-methyl-2-thiophenecarboxaldehyde (540 mg, 4.28 mmol) were treated as described above. The crude product was purified by cc eluting with hexanes/EtOAc (7:3) to yield **32** (yellow solid, 820 mg, 56%), mp 132–133 °C. IR (neat) 2959, 1651, 1592, 1494, 1453, 1293, 1273, 1156, 1116, 967, 863, 829 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.01 (1H, d, J = 15.0 Hz), 7.91 (1H, d, J = 9.0 Hz), 7.78 (1H, s), 7.28 (1H, d, J = 15.0 Hz), 7.26 (1H, d, J = 9.0 Hz), 6.90 (2H, m), 3.83 (2H, s), 3.79 (4H, s), 2.64 (4H, s), 2.39 (3H, s). ^{13}C NMR ($CDCl_3$,100 MHz): δ 187.8, 162.1, 142.4, 134.8, 134.6, 131.3, 1306, 130.5, 130.0, 127.0, 119.6, 119.3, 116.3, 66.1 (2×), 60.5, 52.5 (2×), 14.2. EIMS, *m/z* (% rel. intensity): 343 (100) $[M]^+$, 296 (21), 258 (26), 257 (12), 256 (17), 241 (10), 228 (9), 151 (8), 135 (6), 121 (6), 86 (20), 56 (5). HREIMS *m/z* calcd for $C_{19}H_{21}NO_3S$, 343.1242; found, 343.1241. Elemental analysis: calcd C, 66.45; H, 6.16; N, 4.08; S, 9.34; found, C, 66.60; H, 6.20; N, 4.01; S, 9.42.

5.3.25. (*E*)-1-[4-Hydroxy-3,5-bis(morpholinomethyl)phenyl]-3-(pyridin-2-yl)prop-2-en-1-one (33)

Compound **6b** (1.0 g, 3.09 mmol) and 2-pyridinecarboxaldehyde (380 mg, 3.55 mmol) were treated as described above. The crude product was purified by cc eluting with $CHCl_3$/MeOH (9:1) to yield **33** (pale yellow solid, 940 mg, 74%), mp 152–153 °C. IR (neat) 2957, 1658, 1612, 1592, 1432, 1326, 1162, 1116, 1070, 984, 906, 863, 783 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.67 (1H, d, J = 3.0 Hz), 8.12 (1H, d, J = 15.3 Hz), 7.94 (2H, s), 7.75 (1H, d, J = 15.3 Hz), 7.72 (1H, dd, J = 1.5, 7.8 Hz), 7.53 (1H, d, J = 7.8 Hz), 7.29 (1H, dd, J = 1.5, 3.0 Hz), 3.76 (12H, m), 2.60 (8H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 188.3, 161.4, 153.3, 150.0, 142.0, 136.9, 131.0 (2×), 129.1, 125.3, 125.2, 124.2, 121.6, 66.4 (4×), 58.8 (2×), 52.9 (4×). EIMS, *m/z* (% rel. intensity): 423 (31) $[M]^+$, 365 (7), 337 (36), 336 (100), 278 (14), 253 (50), 252 (46), 251 (46), 222 (20), 194 (18), 132 (16), 100 (28), 86 (15), 57 (14). HREIMS *m/z* calcd for $C_{24}H_{29}N_3O_4$, 423.2158; found, 423.2160. Elemental analysis: calcd C, 68.06; H, 6.90; N, 9.92; found, C, 68.03; H, 6.96; N, 9.90.

5.3.26. (*E*)-1-[4-Hydroxy-3,5-bis(morpholinomethyl)phenyl]-3-(3-methylthiophen-2-yl)prop-2-en-1-one (34)

Compound **6b** (1.0 g, 3.04 mmol) and 3-methyl-2-thiophenecarboxaldehyde (400 mg, 3.17 mmol) were treated as described above. The crude product was purified by cc eluting with $CHCl_3$/MeOH (8:2) to yield **34** (yellow solid, 850 mg, 65%), mp 146–147 °C. IR (neat) 2957, 1631, 1601, 1553, 1473, 1454, 1412, 1370, 1348, 1266, 1160, 1115, 1015, 967, 864 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.01 (1H, d, J = 15.3 Hz), 7.87 (2H, s), 7.31 (1H, d, J = 15.3 Hz), 7.29 (1H, d, J = 4.8 Hz), 6.90 (1H, d, J = 4.8 Hz), 3.78 (12H, br s), 2.62 (8H, s), 2.40 (3H, s). ^{13}C NMR ($CDCl_3$,75 MHz): δ 187.9, 161.0, 142.3, 134.8, 134.7, 131.3 (2×), 130.7, 130.3, 129.5, 127.1, 119.5 (2×), 66.3 (4×), 58.7 (2×), 52.8 (4×), 14.2. EIMS, *m/z* (% rel. intensity): 442 (38) $[M]^+$, 384 (9), 357 (27), 356 (35), 355 (100), 297 (13), 270 (14), 244 (13), 171 (11), 151 (20), 147 (12), 123 (11), 86 (16), 57 (18). HREIMS *m/z* calcd for $C_{24}H_{30}N_2O_4S$, 442.1926; found, 442.1926. Elemental analysis: calcd. 65.13; H, 6.83; N, 6.33; S, 7.25; found, C, 65.03; H, 6.82; N, 6.26; S, 7.30.

5.3.27. (*E*)-1-[3-Hydroxy-4-(morpholinomethyl)phenyl]-3-(pyridin-2-yl)prop-2-en-1-one (35)

Compound **7a** (1.0 g, 4.26 mmol) and 2-pyridinecarboxaldehyde (520 mg, 4.86 mmol) were treated as described above. The crude product was purified by cc eluting with hexanes/EtOAc (7:3) to yield **35** (yellow solid, 850 mg, 62%), mp 114–115 °C. IR (neat) 2958, 1661, 1612, 1574, 1442, 1385, 1320, 1280, 1195, 1116, 991, 865, 775 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.69 (1H, d, J = 4.2 Hz), 8.05 (1H, d, J = 15.0 Hz), 7.76 (1H, d, J = 15.0 Hz), 7.75 (1H, d, J = 1.5 Hz), 7.56 (1H, s), 7.53 (1H, d, J = 1.2 Hz), 7.49 (1H, d, J = 7.8 Hz), 7.30 (1H, m), 7.18 (1H, d, J = 7.8 Hz), 3.84 (2H, s), 3.81 (4H, s), 2.67 (4H, s). ^{13}C NMR ($CDCl_3$,75 MHz): δ 190.0, 157.7, 153.2, 150.0, 142.6, 138.8, 136.8, 129.2, 125.6 (2×), 125.2, 124.3, 119.8, 116.2, 66.4 (2×), 61.2, 52.8 (2×). EIMS, *m/z* (% rel. intensity): 324 (73) $[M]^+$, 285 (20), 277 (29), 239 (100), 238 (81), 237 (68), 209 (27), 208 (53), 180 (19), 161 (16), 132 (14), 106 (14), 93 (47), 86 (21), 78 (15). HREIMS *m/z* calcd for $C_{19}H_{20}N_2O_3$, 324.1474; found, 324.1473. Elemental analysis: calcd C, 70.35; H, 6.21; N, 8.64; found, C, 69.28; H, 6.20; N, 8.33.

5.3.28. (*E*)-1-[3-Hydroxy-4-(morpholinomethyl)phenyl]-3-(pyridin-3-yl)prop-2-en-1-one (36)

Compound **7a** (1.0 g, 4.26 mmol) and 3-pyridinecarboxaldehyde (520 mg, 4.86 mmol) were treated as described above. The crude product was purified by cc eluting with $CHCl_3$/MeOH (9.5:0.5) to yield **36** (yellow solid, 820 mg, 59%), mp 140–141 °C. IR (neat) 2970, 1661, 1603, 1569, 1510, 1450, 1385, 1306, 1270, 1191, 1168, 1116, 985, 864, 764 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.83 (1H, s), 8.62 (1H, d, J = 2.4 Hz), 7.94 (1H, d, J = 7.8 Hz), 7.76 (1H, d, J = 15.6 Hz), 7.55 (1H, d, J = 15.6 Hz), 7.52 (2H, s), 7.34 (1H, m), 7.17 (1H, d, J = 8.1 Hz), 3.81 (6H, m), 2.63 (4H, s). ^{13}C NMR ($CDCl_3$,100 MHz): δ 189.3, 157.8, 151.0, 149.9, 140.7, 138.7, 134.5, 130.7, 129.3, 125.8, 123.9, 123.7, 119.6, 116.1, 66.5 (2×), 61.4, 52.8 (2×). EIMS, *m/z* (% rel. intensity): 324 (100) $[M]^+$, 293 (8), 277 (39), 271 (8), 239 (59), 238 (84), 210 (13), 208 (7), 180 (21), 167 (14), 165 (6), 132 (26), 104 (29), 86 (18), 78 (21), 77 (34), 56 (20). HREIMS *m/z* calcd for $C_{19}H_{20}N_2O_3$, 324.1474; found, 324.1474. Elemental analysis: calcd C, 70.35; H, 6.21; N, 8.64; found, C, 70.24; H, 6.21; N, 8.61.

5.3.29. (*E*)-1-[3-Hydroxy-4-(morpholinomethyl)phenyl]-3-(pyridin-4-yl)prop-2-en-1-one (37)

Compound **7a** (1.0 g, 4.26 mmol) and 4-pyridinecarboxaldehyde (530 mg, 4.95 mmol) were treated as described above. The crude product was purified by cc eluting with disopropyl ether/MeOH (7:3) to yield **37** (yellow solid, 900 mg, 65%), mp 174–175 °C. IR (neat) 2948, 1660, 1610, 1573, 1511, 1393, 1301, 1272, 1171, 1115, 980, 866, 563 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 8.66 (2H, d, J = 6.0 Hz), 8.08 (1H, d, J = 15.3 Hz), 7.82 (2H, d, J = 6.0 Hz), 7.64 (1H, d, J = 15.3 Hz), 7.62 (1H, m), 7.49 (1H, s), 7.35 (1h, d, J = 9.0 Hz), 3.67 (2H, s), 3.61 (4H, s), 2.47 (4H, m). ^{13}C NMR (DMSO-d_6,75 MHz): δ 188.8, 158.9, 150.4 (2×), 141.9, 140.7, 137.2, 129.9, 128.8, 126.5, 122.5 (2×), 119.8, 114.8, 66.1 (2×), 58.1, 52.9 (2×). EIMS, *m/z* (% rel. intensity): 324 (60) $[M]^+$, 293 (5), 284 (18), 277 (24), 271 (5), 239 (100), 238 (52), 210 (12), 180 (12), 167 (9), 153 (7), 132 (14), 104 (13), 97 (13), 77 (22), 71 (22), 69 (22), 55 (19). HREIMS *m/z* calcd for $C_{19}H_{20}N_2O_3$, 324.1474; found, 324.1472. Elemental analysis: calcd C, 70.35; H, 6.21; N, 8.64; found, C, 70.47; H, 6.23; N, 8.65.

5.3.30. (*E*)-3-(Furan-2-yl)-1-[3-hydroxy-2-(morpholinomethyl)-phenyl]prop-2-en-1-one (38)

Compound **7b** (1.0 g, 4.26 mmol) and 2-furaldehyde (420 mg, 4.37 mmol) were treated as described above. The crude product was purified by cc eluting with diisopropyleter/MeOH (7:3) to yield **38** (yellow solid, 1.2 g, 90%), mp 82–83 °C. IR (neat) 2960, 1660, 1581, 1549, 1497, 1455, 1305, 1284, 1269, 1166, 1117, 1070, 985, 865, 793 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.52 (1H, br s), 7.24 (2H, t, J = 9.0 Hz), 7.00 (1H, d, J = 9.0 Hz), 6.99 (H, d, J = 15.0 Hz), 6.96 (1H, d, J = 15.0 Hz), 6.68 (1H, d, J = 2.1 Hz), 6.50 (1H, br s), 3.88 (2H, s), 3.74 (4H, s), 2.59 (4H, s). ^{13}C NMR ($CDCl_3$,75 MHz): δ 195.1, 158.8, 150.9, 145.4, 140.1, 132.1, 128.3, 123.8, 119.1, 118.8 (2×), 116.5, 112.7, 66.4 (2×), 57.6, 52.5 (2×). EIMS, *m/z* (% rel. intensity): 313 (92) $[M]^+$, 284 (11), 228 (18), 227 (30), 226 (100), 210 (12), 198 (12), 197 (34), 191 (12), 190 (22), 161 (14), 147 (44), 141 (15), 121 (12), 115 (14), 86 (56), 81 (30), 56 (17). HREIMS *m/z* calcd for $C_{18}H_{19}NO_4$, 313.1314; found, 313.1313. Elemental analysis: calcd C, 68.21; H, 5.72; N, 4.68; found, C, 68.73; H, 6.09; N, 4.50.

5.3.31. (*E*)-1-[3-Hydroxy-2-(morpholinomethyl)phenyl]-3-(thiophen-2-yl)prop-2-en-1-one (39)

Compound **7b** (1.0 g, 4.26 mmol) and 2-thiophenecarboxaldehyde (480 mg, 4.28 mmol) were treated as described above. The crude product was purified by cc eluting with hexanes/EtOAc (7:3) to yield **39** as yellow oil (1.2 g, 86%). IR (neat) 2960, 1638, 1581, 1498, 1454, 1286, 1166, 1116, 984, 933, 863, 792 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.60 (1H, d, J = 15.6 Hz), 7.46 (1H, d, J = 3.6 Hz), 7.31 (1H, d, J = 3.6 Hz), 7.23 (1H, d, J = 9.0 Hz), 7.08 (1H, d, J = 9.0 Hz), 7.02 (1H, m), 6.98 (1H, s), 6.91 (1H, d, J = 15.6 Hz), 3.91 (2H, s), 3.77 (4H, s), 2.64 (4H, s). ^{13}C NMR ($CDCl_3$,75 MHz): δ 195.0, 158.8, 140.1, 139.7, 138.9, 132.3, 129.7, 128.9, 128.4, 125.1, 119.6 (2×), 118.2, 66.0 (2×), 56.8, 52.4 (2×). EIMS, *m/z* (% rel. intensity): 329 (68) $[M]^+$, 244 (32), 243 (35), 242 (100), 213 (24), 190 (22), 181 (10), 147 (42), 134 (13), 109 (13), 97 (40), 86 (70), 58 (42), 57 (19). HREIMS *m/z* calcd for $C_{18}H_{19}NO_3S$, 329.1086; found, 329.1083. Elemental analysis: calcd C, 66.45; H, 6.16; N, 4.08; S, 9.34; found, C, 66.49; H, 5.95; N, 4.12; S, 9.79.

5.3.32. (*E*)-1-[3-Hydroxy-2-(morpholinomethyl)phenyl]-3-(3-methylthiophen-2-yl)prop-2-en-1-one (40)

Compound **7b** (1.0 g, 4.26 mmol) and 3-methyl-2-thiophenecarboxaldehyde (540 mg, 4.28 mmol) were treated as described above. The crude product was purified by cc eluting with diispropylether/MeOH (7:3) to yield **40** (yellow solid, 1.0 g, 66%), mp 101–102 °C. IR (neat) 2959, 1655, 1603, 1576, 1499, 1454, 1286, 1166, 1116, 1069, 984, 864 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.75 (1H, d, J = 15.6 Hz), 7.33 (1H, d, J = 5.1 Hz), 7.28 (1H, d, J = 15.6 Hz), 7.04 (1H, d, J = 9.0 Hz), 6.98 (1H, d, J = 9.0 Hz), 6.90 (1H, d, J = 3.9 Hz), 6.82 (1H, d, J = 9.0 Hz), 3.93 (2H, s), 3.77 (4H, s), 2.63 (4H, s), 2.32 (3H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 194.6, 158.8, 143.1, 140.5, 136.9, 134.0, 131.5, 128.8, 128.2, 123.8, 119.5 (2×), 118.5, 66.2 (2×), 57.0, 52.5 (2×), 14.3. EIMS, *m/z* (% rel. intensity): 343 (87) $[M]^+$, 258 (30), 257 (34), 256 (100), 243 (16), 227 (18), 213 (17), 190 (37), 161 (21), 147 (24), 127 (46), 126 (61), 111 (83), 86 (51), 77 (25), 57 (16). HREIMS *m/z* calcd for $C_{19}H_{21}NO_3S$, 343.1242; found, 343.1245. Elemental analysis: calcd C, 65.63; H, 5.81; N, 4.25; S, 9.73; found, C, 66.23; H, 6.18; N, 3.96; S, 9.72.

5.3.33. (*E*)-1-[3-Hydroxy-2-(morpholinomethyl)phenyl]-3-phenylprop-2-en-1-one (41)

Compound **7b** (1.0 g, 4.26 mmol) and benzaldehyde (440 mg, 4.15 mmol) were treated as described above. The crude product was purified by cc eluting with diisopropylether/MeOH (8:2) to yield **41** (brown solid, 1.0 g, 73%), mp 71–72 °C. IR (neat) 2961, 1642, 1578, 1497, 1453, 1402, 1166, 1117, 1070, 986, 933, 797, 762 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.55 (2H, m), 7.46 (1H, d, J = 16.2 Hz), 7.40 (3H, m), 7.25 (1H, t, J = 7.8 Hz), 7.10 (1H, d, J = 16.2 Hz), 6.99 (2H, t, J = 7.8 Hz), 3.87 (2H, s), 3.74 (4H, s), 2.57 (4H, m). ^{13}C NMR ($CDCl_3$,100 MHz): δ 195.8, 158.8, 146.2, 140.1,

134.2, 130.8, 128.9 (2×), 128.4 (3×), 126.6, 119.1, 118.8 (2×), 66.4 (2×), 57.6, 52.5 (2×). EIMS, *m/z* (% rel. intensity): 323 (38) $[M]^+$, 322 (11), 238 (37), 237 (39), 236 (85), 235 (61), 207 (20), 190 (21), 178 (15), 162 (23), 148 (100), 147 (42), 131 (19), 103 (21), 91 (30), 86 (74), 77 (29), 57 (19). HREIMS *m/z* calcd for $C_{20}H_{21}NO_3$, 323.1521; found, 323.1520. Elemental analysis: calcd C, 74.28; H, 6.55; N, 4.33; found, 73.94; H, 6.63; N, 4.35.

5.3.34. (*E*)-1-[3-Hydroxy-2,4-bis(morpholinomethyl)phenyl]-3-(pyridin-2-yl)prop-2-en-1-one (42)

Compound **7c** (1.0 g, 3.09 mmol) and 2-pyridinecarboxaldehyde (380 mg, 3.55 mmol) were treated as described above. The crude product was purified by cc eluting with $CHCl_3$/MeOH (9:1) to yield **42** (brown solid, 850 mg, 67%), mp 117–118 °C. IR (neat) 2957, 1649, 1613, 1573, 1503, 1435, 1306, 1116, 986, 863 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.61 (1H, d, J = 3.0 Hz), 7.70 (1H, t, J = 7.5 Hz), 7.47 (1H, d, J = 15.3 Hz), 7.46 (1H, d, J = 7.5 Hz), 7.34 (1H, m), 7.25 (1H, d, J = 15.3 Hz), 7.12 (1H, d, J = 7.8 Hz), 3.75 (6H, s), 3.68 (2H, s), 3.60 (4H, s), 2.57 (4H, s), 2.45 (4H, s). ^{13}C NMR ($CDCl_3$,100 MHz): δ 195.8, 156.5, 153.3, 150.1, 142.2, 139.9, 136.7, 130.7, 128.4, 124.1, 123.9 (2×), 121.4, 118.9, 66.5 (2×), 66.3 (2×), 59.2, 54.7, 53.0 (2×), 52.6 (2×). EIMS, *m/z* (% rel. intensity): 423 (2) $[M]^+$, 339 (7), 338 (31), 336 (62), 252 (21), 251 (100), 250 (30), 249 (31), 248 (60), 232 (20), 223 (20), 222 (19), 204 (10), 194 (12). HREIMS *m/z* calcd for $C_{24}H_{29}N_3O_4$, 423.2158; found, 423.2161. Elemental analysis: calcd C, 68.06; H, 6.90; N, 9.92; found, C, 67.81; H, 6.88; N, 9.85.

5.3.35. (*E*)-3-[3-Hydroxy-4-methoxy-2-(morpholinomethyl)-phenyl]-1-*m*-tolylprop-2-en-1-one (43)

Compound **8b** (1.90 g, 7.57 mmol) and 3-methylacetophenone (1.02 g, 7.61 mmol) were treated as described above. The crude product was purified by cc eluting with disopropylether/MeOH (7:3) to yield **43** (yellow solid, 2.01 g, 75%), mp 114–115 °C. IR (neat) 2957, 1656, 1604, 1581, 1462, 1403, 1257, 1181, 1116, 1075, 1040, 1004, 864, 800 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ9.41 (1H, s, OH), 8.08 (1H, d, J = 15.3 Hz), 7.87 (2H, m), 7.58 (1H, d, J = 15.3 Hz), 7.49 (1H, d, J = 9.0 Hz), 7.43 (2H, m), 6.95 (1H, d, J = 9.0 Hz), 3.83 (3H, s), 3.73 (2H, s), 3.52 (4H, m), 2.43 (7H, m). ^{13}C NMR (DMSO-d_6,75 MHz): δ 198.8, 148.3, 145.2, 141.6, 141.6, 137.2 (2×), 132.4, 127.9, 127.6, 126.5, 124.7, 122.0, 120.0, 117., 109., 65.3 (2×), 54.8, 52.5, 51.7 (2×), 20.0. EIMS, *m/z* (% rel. intensity): 367 (8) $[M]^+$, 313 (92), 284 (11), 227 (30), 226 (100), 210 (13), 197 (34), 190 (22), 169 (16), 147 (44), 141 (15), 115 (14), 86 (56), 81 (30). HREIMS *m/z* calcd for $C_{22}H_{25}NO_4$, 367.1784; found, 367.1785. Elemental analysis: calcd C, 71.91; H, 6.86; N, 3.81; found, C, 71.53; H, 6.88; N, 3.86.

5.3.36. (*E*)-3-[3-Hydroxy-4-methoxy-2-(morpholinomethyl)-phenyl]-1-*p*-tolylprop-2-en-1-one (44)

Compound **8b** (1.90 g, 7.57 mmol) and 4-methylacetophenone (1.02 g, 7.61 mmol) were treated as described above. The crude product was purified by cc eluting with disopropylether/MeOH (7:3) to yield **44** (yellow solid, 2.3 g, 83%), mp 137–138 °C. IR (neat) 2957, 1657, 1579, 1463, 1400, 1258, 1162, 1117, 1002, 863, 796 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 9.94 (1H, s, OH), 8.07 (1H, d, J = 15.6 Hz), 7.99 (2H, d, J = 8.1 Hz), 7.58 (1H, d, J = 15.6 Hz), 7.49 (1H, d, J = 8.7 Hz), 7.34 (2H, d, J = 8.1 Hz), 6.95 (1H, d, J = 8.7 Hz), 3.85 (3H, s), 3.72 (2H, s), 3.53 (4H, s), 2.42 (4H, s), 2.38 (3H, s). ^{13}C NMR (DMSO-d_6,75 MHz): δ 188.1, 148.2, 145.2, 142.2, 141.3, 134.5, 128.3 (2×), 127.6 (2×), 126.5, 121.9, 120.4, 117.8, 109.8, 65.3 (2×), 54.8, 52.5, 51.8 (2×), 20.2. EIMS, *m/z* (% rel. intensity): 367 (18) $[M]^+$, 282 (23), 280 (10), 248 (42), 190 (9), 162 (13), 119 (100), 105 (9), 91 (31), 86 (12). HREIMS *m/z* calcd for $C_{22}H_{25}NO_4$, 367.1784; found, 367.1786. Elemental analysis: calcd C, 71.91; H, 6.86; N, 3.81; found, C, 71.90; H, 6.86; N, 3.69.

5.3.37. (*E*)-3-[3-Hydroxy-4-methoxy-2-(piperidin-1-ylmethyl)-phenyl]-1-(thiophen-2-yl)prop-2-en-1-one (45)

Compound **8a** (1.0 g, 4.01 mmol) and 2-acetylthiophene (504 mg, 4.01 mmol) were treated as described above. The crude product was purified by cc eluting with hexanes/EtOAc (8:2) to yield **45** (pale yellow solid, 1.3 g, 91%), mp 123–124 °C. IR (neat) 2937, 1645, 1576, 1513, 1472, 1412, 1355, 1257, 1078, 751, 664 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.05 (1H, d, J = 15.3 Hz), 7.83 (1H, d, J = 3.0 Hz), 7.71 (1H, d, J = 3.0 Hz), 7.22 (1H, d, J = 15.3 Hz), 7.19 (1H, d, J = 9.0 Hz), 7.09 (1H, dd, J = 3.0, 3.0 Hz), 3.91 (2H, s), 3.90 (3H, s), 2.58 (4H, s), 1.64 (4H, s), 1.49 (2H, s). ^{13}C NMR ($CDCl_3$,75 MHz): δ 182.3, 150.5, 148.9, 146.1, 141.5, 134.2, 132.1, 128.7, 127.0, 122.2, 121.4, 118.4, 111.1, 57.9, 56.3, 54.3, 26.1, 24.2. EIMS, *m/z* (% rel. intensity): 357 (35) $[M]^+$, 274 (10), 246 (48), 229 (4), 190 (7), 163 (8), 162 (14), 147 (6), 111 (100), 97 (10), 84 (69). HREIMS *m/z* calcd for $C_{20}H_{23}NO_3S$, 357.1399; found, 357.1402. Elemental analysis: calcd C, 67.20; H, 6.49; N, 3.92; S, 8.97; found, C, 67.11;, 6.46; N, 3.87; S, 9.20.

5.3.38. (*E*)-1-(Furan-2-yl)-3-[3-hydroxy-4-methoxy-2-(piperidin-1-ylmethyl)phenyl]prop-2-en-1-one (46)

Compound **8a** (1.0 g, 4.01 mmol) and 2-acetylfuran (450 mg, 4.09 mmol) were treated as described above. The crude product was purified by cc eluting with hexanes/EtOAc (8:2) to yield **46** (yellow solid, 1.1 g, 81%), mp 155–156 °C. IR (neat) 2937, 1654, 1581, 1465, 1403, 1263, 1081, 1050, 985, 927, 757 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.06 (1H, d, J = 15.3 Hz), 7.64 (1H, s), 7.31 (1H, d, J = 3.0 Hz), 7.29 (1H, d, J = 15.3 Hz), 7.26 (1H, d, J = 9.0 Hz), 6.84 (1H, d, J = 9.0 Hz), 6.58 (1H, t, J = 3.0 Hz), 4.00 (2H, s), 3.91 (3H, s), 2.66 (4H, s), 1.70 (4H, s), 1.51 (2H, s). ^{13}C NMR ($CDCl_3$,100 MHz): δ 177.7, 153.7, 150.3, 148.1, 146.5, 140.6, 126.7, 121.4, 120.6, 118.3, 117.4, 112.5, 110.8, 56.3, 55.8, 53.7, 25.1, 23.4. EIMS, *m/z* (% rel. intensity): 341 (61) $[M]^+$, 258 (13), 256 (11), 246 (54), 227 (6), 190 (5), 177 (11), 162 (24), 161 (14), 95 (100), 84 (92), 81 (11). HREIMS *m/z* calcd for $C_{20}H_{23}NO_4$, 341.1627; found, 341.1628. Elemental analysis: calcd C, 70.36; H, 6.79; N, 4.10; found, C, 70.31; H, 6.85; N, 4.09.

5.3.39. (*E*)-3-[3-Hydroxy-4-methoxy-2-(piperidin-1-ylmethyl)phenyl]-1-(pyridin-3-yl)prop-2-en-1-one (47)

Compound **8a** (1.0 g, 4.01 mmol) and 3-acetylpyridine (490 mg, 4.05 mmol) were treated as described above. The crude product was purified by cc eluting with diisopropylether/MeOH (8:2) to yield **47** (yellow solid, 920 mg, 65%), mp 112–113 °C. IR (neat) 2936, 1659, 1583, 1470, 1407, 1347, 1307, 1258, 1155, 1110, 1077, 982, 861 795, 753 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 9.24 (1H, s), 8.80 (1H, d, J = 4.2 Hz), 8.30 (1H, d, J = 7.8 Hz), 8.12 (1H, d, J = 15.3 Hz), 7.46 (1H, t, J = 6.9 Hz), 7.35 (1H, d, J = 15.3 Hz), 7.31 (1H, d, J = 8.4 Hz), 6.87 (1H, d, J = 8.4 Hz), 3.99 (2H, s), 3.93 (3H, s), 2.65 (4H, s), 1.72 (4H, s), 1.52 (2H. s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 188.4, 152.9, 150.2, 149.5, 148.4, 142.6, 135.7, 133.5, 126.1, 123.5, 121.0, 120.9, 118.0, 110.5, 57.3, 55.7, 53.7, 25.5, 23.6. EIMS, *m/z* (% rel. intensity): 352 (44) $[M]^+$, 269 (20), 246 (79), 164 (24), 162 (16), 147 (15), 106 (77), 84 (100), 78 (56). HREIMS *m/z* calcd for $C_{21}H_{24}N_2O_3$, 352.1787; found, 352.1790. Elemental analysis: calcd C, 71.57; H, 6.86; N, 7.95; found, C, 71.38; H, 6.93; N, 7.85.

5.4. Cytotoxic activity assay

All stock cultures were grown in T-25 flasks. Freshly trypsinized cell suspensions were seeded in 96-well microtiter plates at densities of 1500–7500 cells per well with compounds added from DMSO-diluted stock. After 3 days in culture, attached cells were fixed with cold 50% trichloroacetic acid and then stained with 0.4% sulforhodamine B (SRB). The absorbance at 562 nm

was measured using a microplate reader after solubilizing the bound dye. The mean EC_{50} is the concentration of agent that reduces cell growth by 50% under the experimental conditions and is the average from at least three independent determinations that were reproducible and statistically significant. The following human tumor cell lines were used in the assay: PC-3 (prostate cancer), MCF-7 (human breast cancer), KB (nasopharyngeal carcinoma), and KB-VIN (vincristine-resistant KB subline). All cell lines were obtained from the Lineberger Comprehensive Cancer Center (UNC-CH) or from ATCC (Rockville, MD) and were cultured in RPMI-1640 medium supplemented with 25 μM HEPES, 0.25% sodium bicarbonate, 10% fetal bovine serum, and 100 μg/mL kanamycin.[30]

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